 

# Stereochemistry and Stereoisomerism Characterized by the Sphericity Concept

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The sphericity concept proposed for specifying stereochemistry in a molecule (S. Fujita, *J. Am. Chem. Soc.*, **112**, 3390 (1990)) has been extended to investigate stereoisomerism among molecules. The new matter of the present approach is to characterize the global symmetries of molecules as the "local symmetries of stereoisomerism". Thereby, stereochemistry and stereoisomerism have been discussed on a common basis. Promolecules, which have been generated as stereochemical models of molecules by placing proligands (structureless ligands with chirality/achirality) on the vertices of a tetrahedral skeleton, have been analyzed by a permutation-group approach as well as by a point-group one. The skeleton has been considered to belong to the symmetric group of degree 4 ($\mathbf{S}^{[4]}$) as well as to the isomorphic point group $\mathbf{T}_d$. The chirality fittingness derived from the sphericity concept has been applied to the characterization of local symmetries of promolecule, where two types of Young's tableaus have been compared. Thus, Young's tableaus of symmetry have been introduced to treat the ligand packing based on the chirality fittingness. These tableaus have been compared with Young's tableaus of permutation, which have taken no account of such chirality fittingness. The two types of Young's tableaus have been applied to the enumeration of tetrahedral isomers under the observance and the violation of chirality fittingness. This enumeration has enabled us to clarify the quantitative aspect of the sphericity concept in characterizing isomer equivalence. Thereby, equivalent isomers under a point-group symmetry have been shown to construct an orbit of stereoisomers that is ascribed to a coset representation. Homomeric, enantiomeric, and diastereomeric relationships between stereoisomers have been discussed by means of homospheric, enantiospheric and hemispheric orbits of stereoisomers. Skeleton-based and ligand-based categories for enantiomers and diastereomers have been discussed. The stereogenicity and the prostereogenicity of the Chan–Ingold–Prelog system have been related to Young's tableaus of permutation.

A tetrahedral model proposed by van't Hoff[1,2] has been the foundation of organic stereochemistry, where a set of atoms or substituents have been considered to be placed on the vertices of the tetrahedral skeletons. The term "asymmetric carbon center" has been a key of classifying stereoisomers, though it has sometimes provided organic chemists and biochemists with serious confusion.[3] Since the term does not always correspond to the chirality of a molecule, another term "pseudoasymmetric" has later been coined to designate an apparent asymmetric carbon that does not show optical activity.[4] The sequence rule proposed by Cahn, Ingold, and Prelog (the CIP system)[5] and its application to the "prochirality" by Hanson[6] have necessitated more logical descriptions of asymmetric and pseudoasymmetric carbons. Prelog and Helmchen[7] have defined the terms "prochiral, pseudoasymmetric, and propseudoasymmetric centers" on the basis of partition diagrams (Young's tableaus), which in themselves did not succeed in explaining several point-group symmetries such as those for meso-compounds.[8–10] The prochirality term has been revised by Hirschmann and Hanson[11,12] and has been adopted by IUPAC as Rule E-4.12(b).[13–15] However, the IUPAC rule has been accompanied with Rule E-4.12(a) as another definition of prochirality,[15] which provides us with results distinct from those available from the Rule E-4.12(b).[16,17] The polysemy of the prochirality has provided serious confusion in discussing stereochemical problems, as pointed out previously.[17] Moreover, the usage of such terms as "elements of chirality" and "elements of prochirality" has been a source of contention ever since.[18–20] In order to clarify such chirality and prochirality, the relationship between two sites of a molecule, i.e., stereochemical equivalence or non-equivalence, should be examined. For this purpose, the topicity terms ("enantiotopic" and "diastereotopic") introduced by Mislow and Raban[21] have been used conveniently and successfully. Another term, "equitopic" (by Nakazaki[22,23]) or "homotopic" (by Hirschmann and Hanson[11]), has later been added for the sake of consistent description. These topicity terms and the related prochirality terms have been widely accepted by organic chemists and biochemists, as described in various reviews[24–27] and textbooks.[28–30] In these approaches, the chirality and the prochirality of a molecule, which are concerned with global symmetry or stereoisomerism, have been presumed to be derived in a straightforward manner from the stereochemistry (local symmetry) of subunits contained in the molecule. However, the relationship between the global symmetry and the local symmetry has not been so fully solved as to settle all contentions. This situation has stemmed from the lack of an appropriate mathematical or logical framework dealing with both global and local symme-

tries.

Mislow and Siegel[31] have discussed the items described in the preceeding paragraph under the paradoxical title "stereochemistry without stereoisomerism". This title has indicated that they have put emphasis on local symmetries but not on global symmetries, since the stereoisomerism is concerned with the global symmetries of molecules. Thus they have emphasized local chirality in proposing the term "chirotopic". As a result, organic chemists and biochemists now use two distinct kinds of topic terms, i.e. the terms for stereochemical *relathionships* ("homotopic", "enantiotopic", and "diastereotopic") and the terms for stereochemical *attributes* ("chirotopic" and "achirotopic"). Such usage has resulted in two connotations for the suffix "topic" so that dual expressions such as "homotopic and chirotopic" and "homotopic and achirotopic" are necessary to characterize the sites of chiral and achiral molecules precisely, whereas the expression "enantiotopic and chirotopic" is not necessary because "enantiotopic" relationships imply "chirotopic" attributes in achiral molecules. Such puzzling situations should be settled in order to reach more comprehensive insights into stereochemistry.[32–34] The importance of local (site) symmetries in other contexts has been reported by Flurry[35] and by Pople.[36] Obviously, the approaches described in this paragraph have put emphasis on local symmetries but not on global symmetries.

Mislow and Siegel[31] have also given convincing arguments to abandon the terms "elements of chirality" and "elements of prochirality". In place of these terms, they have recommended the use of the terms "stereogenic" and "prostereogenic" proposed earlier by McCasland.[37] The latter terms have been adopted in the revised CIP system in the form of the descriptors of stereogenic units etc.[38–41] Thus, the CIP-system has used three types of the stereogenic units, i.e. the chirality center, the chirality plane, and the chirality axis; as well as the analogous "pseudoasymmetric" stereogenic units, i.e. the pseudoasymmetric center, the pseudoasymmetric plane, and the pseudoasymmetric axis.[38] However, the adoption of the terms "stereogenic" and "prostereogenic" in place of the "chirality" of the original CIP system[5] and Hanson's "prochirality"[6] has provided us only with an apparent settlement of the contention, because the mathematical or logical meanings of the terms have not yet been clarified.

A tetrahedral model has been alternatively discussed by Ruch and co-workers to formulate chirality functions on the basis of the permutation-group theory.[42,43] This model has been extended by Mead to treat chiral ligands.[44] Another permutation-group approach has been explored by Ugi et al. so as to give perspectives in theoretical stereochemistry, where the notations of chemical identity groups and permutation isomerism have provided the foundation for the formalization of stereochemistry.[45–47] Further permutation approaches to dynamic stereochemistry and other chemical fields have been published.[48,49] The configuration symmetry group based on permutation groups has been proposed by Nourse and applied to stereoisomer generation.[50] More recent efforts have been focused on computational generation of stereoisomers, where several subrules have been added to the CIP system.[51,52] The approaches described in this paragraph have dealt mainly with stereoisomerism, or global symmetries in other words; hence they have little considered the local symmetries of molecules.

We have discussed a tetrahedral model in terms of the concept of promolecules,[17,53,54] where we have emphasized the importance of a coset representation (CR) $\mathbf{G}(/\mathbf{G}_i)$ and of its subduction.[55] The target of our approach has been to integrate point groups and permutation groups by virtue of coset representations (CRs).[34] We have coined the sphericity terms and applied them to the redefinition of prochirality,[34] topicity,[56,57] stereogenicity,[57] and anisochrony.[58] Thus, these efforts of ours have been restricted to examine local symmetries, though our approach has the potentiality of investigating both global symmetries and local ones as indicated by the symbol $\mathbf{G}(/\mathbf{G}_i)$. Our previous efforts on global symmetries have been concerned only with isomer enumeration,[55–63] where global symmetries are treated rather implicitly.

As found in the preceding paragraphs, global symmetries and local symmetries should be discussed on a common basis in order to reach a comprehensive understanding on *stereochemistry along with stereoisomerism*. This goal means that the global symmetries of promolecules will be investigated as the "local symmetries of stereoisomerism". For this purpose, the present paper is devoted to a new treatment of a tetrahedral skeleton by means of the symmetric group of degree 4 ($\mathbf{S}^{[4]}$) in comparison with the isomorphic point group $\mathbf{T}_d$. We will introduce two types of Young's tableaus, i.e. those of permutation and those of symmetry. We will then examine the combinatorial enumeration based on the two types of Young's tableaus. Thereby, we will show that the distinction between and the careful comparison between the two types of Young's tableaus are important to comprehend stereochemistry as well as stereoisomerism.

## Results

**1 Sphericity Revisited and Two Types of Young's Tableaus.** Throughout the present paper, we use the sphericity terms in place of the topicity terms in order to show the consistency provided by the sphericity terms. Hence, essential items on the sphericity concept should be revisited briefly here. A set of equivalent positions in a skeleton is called an orbit, which corresponds to a coset representation $\mathbf{G}(/\mathbf{G}_i)$,[34] where the point group $\mathbf{G}$ is the global symmetry of the molecule and the point group $\mathbf{G}_i$ is the local symmetry of each position of the orbit. Note that the $\mathbf{G}_i$ is a subgroup of the $\mathbf{G}$. The coset representation is a kind of permutation representation, the degree of which is calculated to be $|\mathbf{G}|/|\mathbf{G}_i|$ and is equal to the number of the equivalent positions, where $|\mathbf{G}|$ and $|\mathbf{G}_i|$ designate the orders of the groups $\mathbf{G}$ and $\mathbf{G}_i$. Then, the sphericity of the $\mathbf{G}(/\mathbf{G}_i)$-orbit is determined by the criteria listed in Table 1.[34]

Each orbit can accommodate achiral and/or chiral objects (atoms, ligands, or proligands) in agreement with its sphericity so as to produce molecules or promolecules.[53] This selection rule is called *chirality fittingness*, as found in the rightmost column of Table 1. It should be noted that achiral objects in an enantiospheric orbit or in a hemispheric orbit are no longer achiral but are restricted to belong to the corresponding chiral local symmetry. The *prochirality* is ascribed to the presence of at least one enantiospheric orbit.

According to the chirality fittingness, an enantiospheric orbit can accommodate chiral objects in a manner of compensat-

Table 1. Sphericity of $\mathbf{G}(/\mathbf{G}_i)$[34]

| Global symmetry $\mathbf{G}$ | Local symmetry $\mathbf{G}_i$ | Sphericity of $\mathbf{G}(/\mathbf{G}_i)$ | Chirality fittingness (objects allowed) |
|---|---|---|---|
| achiral | achiral | homespheric | achiral |
| achiral | chiral | enantiospheric | achiral, chiral[a)] |
| chiral | chiral | hemispheric | achiral, chiral |

a) A compensated chiral packing of enantiomeric objects of opposite chiralities.

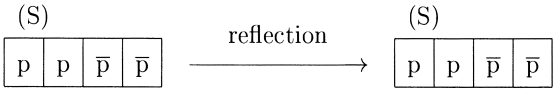



Fig. 1. Compensated chiral packing for an enantiospheric orbit (e.g. $\mathbf{S}_4(/\mathbf{C}_1)$).

ed chiral packing, where one half of an enantiospheric orbit accommodates chiral objects of the same chirality and the other half accommodates chiral objects of the opposite chirality. For example, a compensated chiral packing for an enantiospheric $\mathbf{S}_4(/\mathbf{C}_1)$-orbit[64] is illustrated in Fig. 1 by using Young's tableau, where the symbols p and $\overline{\text{p}}$ represent enantiomeric chiral ligands.[65] According to the enantiosphericity of the orbit, the ligands p and $\overline{\text{p}}$ in the row of the orbit can be permuted with changing chirality into their mirror images on the action of reflections. Thereby, such reflection operations give no apparent changes, as shown in Fig. 1. This type of Young's tableaus is called "Young's tableaus of point-group symmetry" or shortly "Young's tableaus of symmetry" and is designated by the symbol (S), because the manners of permutations are controlled by the chirality fittingness due to point-group symmetries.

On the other hand, the original usage of Young's tableaus takes no account of such chirality fittingness, where any elements in the row can freely be permuted. Such a type of Young's tableaus is called "Young's tableaus of permutation-group symmetry" or shortly "Young's tableaus of permutation" and is designated by the symbol (P) after permutation-group symmetries. It should be emphasized here that the distinction between and the comparison between the two types of Young's tableaus provide us with fruitful discussion.

**2 Ligand Equivalence under Point Groups and under Permutation Groups. 2.1 Point-Group Symmetries.** Let us consider a tetrahedral skeleton belonging to the point group $\mathbf{T}_d$. Its four vertices called "positions" are regarded as constructing an orbit governed by the CR $\mathbf{T}_d(/C_{3v})$.[34,56] Each operation (proper or improper rotation) of $\mathbf{T}_d$ corresponds faithfully to a permutation of the CR $\mathbf{T}_d(/\mathbf{C}_{3v})$, as reported previously.[60] Suppose that the positions are occupied by a set of four proligands so as to give a promolecule. The symmetry of the resulting promolecule is a subgroup of $\mathbf{T}_d$.

**$ABX_2$-Promolecules.** A selected set of proligands symmetrically modifies (or desymmetrizes) the original set of positions, as shown in Fig. 2. For example, a proligand set $ABX_2$, in which the symbols A, B, and X denote achiral proligands, requires a separation of the orbit of four equivalent positions into three sets of equivalent positions (two plus one plus one positions). The process of such desymmetrization is controlled by the subduction of the CR:

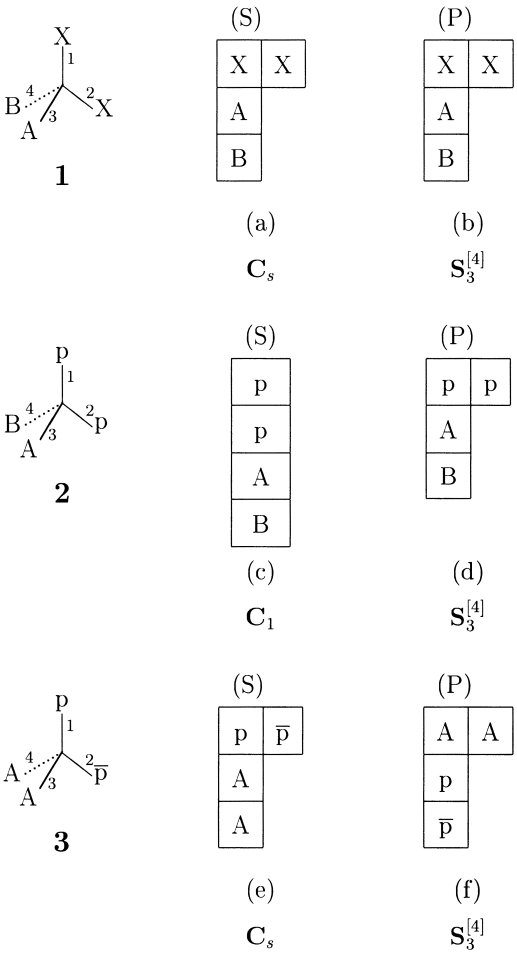


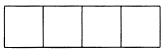
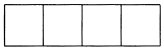
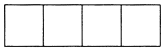
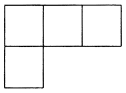
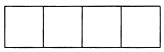
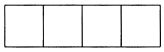
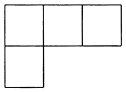
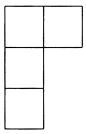
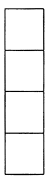

Fig. 2. Ligand packing for $ABX^2$-, $ABp^2$-, and $A^2p\overline{p}$-promolecules under point-group symmetries and under permutation-group symmetries.

$$\mathbf{T}_d(/\mathbf{C}_{3v}) \downarrow \mathbf{C}_s = \mathbf{C}_s(/\mathbf{C}_1) + 2\mathbf{C}_s(/\mathbf{C}_s), \quad (1)$$

as reported by us.[34,56] Since the sizes of a $\mathbf{C}_s(/\mathbf{C}_1)$-orbit and a $\mathbf{C}_s(/\mathbf{C}_s)$-orbit are calculated to be 2 ($= |\mathbf{C}_s|/|\mathbf{C}_1| = 2/1$) and 1 ($= |\mathbf{C}_s|/|\mathbf{C}_s| = 1/1$) respectively, the result on the right-hand side of Eq. 1 is represented by a Young's tableau (cycle structure: $2^1 1^2$) listed in Table 2, where the powers of the cycle structure are the coefficients appearing on the right-hand side of Eq. 1. Note that the rows of the tableau correspond to the orbits. The subductions and related data for the other subgroups of $\mathbf{T}_d$ can be obtained similarly, as summarized in Table 2.

The $\mathbf{C}_s(/\mathbf{C}_1)$-orbit shown in the right-hand side of Eq. 1 ac-

Table 2. Subduction of a $\mathbf{T}_d(/\mathbf{C}_{3v})$-Orbit

| Subgroup of $\mathbf{T}_d$ | Tableau | Cycle structure | Subduction of $\mathbf{T}_d(/\mathbf{C}_{3v})$ | Sphericity | USCI with CF |
|---|---|---|---|---|---|
| $\mathbf{T}_d$ |  | $4^1$ | $\mathbf{T}_d(/\mathbf{C}_{3v})$ | homospheric | $a_4$ |
| $\mathbf{T}$ |  | $4^1$ | $\mathbf{T}(/\mathbf{C}_3)$ | hemispheric | $b_4$ |
| $\mathbf{D}_{2d}$ |  | $4^1$ | $\mathbf{D}_{2d}(/\mathbf{C}_s)$ | homospheric | $a_4$ |
| $\mathbf{C}_{3v}$ |  | $3^1 1^1$ | $\mathbf{C}_{3v}(/\mathbf{C}_s)$<br>$\mathbf{C}_{3v}(/\mathbf{C}_{3v})$ | homospheric<br>homospheric | $a_1 a_3$ |
| $\mathbf{C}_{2v}$ |  | $2^2$ | $\mathbf{C}_{2v}(/\mathbf{C}_s)$<br>$\mathbf{C}_{2v}(/\mathbf{C}'_s)$ | homospheric<br>homospheric | $a^2{}_2$ |
| $\mathbf{D}$ |  | $4^1$ | $\mathbf{D}_2(/\mathbf{C}_1)$ | hemispheric | $b_4$ |
| $\mathbf{S}_4$ |  | $4^1$ | $\mathbf{S}_4(/\mathbf{C}_1)$ | enantiospheric | $c_4$ |
| $\mathbf{C}_3$ |  | $3^1 1^1$ | $\mathbf{C}_3(/\mathbf{C}_1)$<br>$\mathbf{C}_3(/\mathbf{C}_3)$ | hemispheric<br>hemispheric | $b_1 b_3$ |
| $\mathbf{C}_s$ |  | $2^1 1^2$ | $\mathbf{C}_s(/\mathbf{C}_1)$<br>$\mathbf{C}_s(/\mathbf{C}_s)$<br>$\mathbf{C}_s(/\mathbf{C}_s)$ | enantiospheric<br>homospheric<br>homospheric | $a_1{}^2 c_2$ |
| $\mathbf{C}_2$ |  | $2^2$ | $\mathbf{C}_2(/\mathbf{C}_1)$<br>$\mathbf{C}_2(/\mathbf{C}_1)$ | hemispheric<br>hemispheric | $b_2{}^2$ |
| $\mathbf{C}_1$ |  | $1^4$ | $\mathbf{C}_1(/\mathbf{C}_1)$<br>$\mathbf{C}_1(/\mathbf{C}_1)$<br>$\mathbf{C}_1(/\mathbf{C}_1)$<br>$\mathbf{C}_1(/\mathbf{C}_1)$ | hemispheric<br>hemispheric<br>hemispheric<br>hemispheric | $b_1{}^4$ |

commodates two achiral proligands (e.g., $X_2$) because of its enantiosphericity; and each of the $\mathbf{C}_s(/\mathbf{C}_s)$-orbits (homospheric orbits) accommodates one achiral proligand (e.g., A or B) so as to give a promolecule **1** as shown in Fig. 2. The allowed chirality/achirality of each proligand (the chirality fittingness described in Table 1) is restricted by the sphericity of the corresponding CR (Table 2). The ligand packing for **1** is represented by packing (a) in Fig. 2.

**$ABp_2$-Promolecules.** On the other hand, a promolecule (**2**) generated by placing a set of two achiral proligands (A and B) and two chiral proligands of the same kind (p) does not correspond to the packing (a) in which the two X's are replaced by two p's. Note that the two p's cannot occupy the enantiospheric $\mathbf{C}_s(/\mathbf{C}_1)$-orbit because of the chirality fittingness. Instead, a further desymmetrization occurs so as to take the packing (c) shown in Fig. 2. As a result, the promolecule **2** belongs to the point group $\mathbf{C}_1$ (asymmetric), where no symmetry elements are present. The packing (c) ascribed to **2** (Fig. 2) is in agreement with chirality fittingness,[54] although it has two chiral proligands (p) of the same kind. Thus, one ligand p belongs to one $\mathbf{C}_1(/\mathbf{C}_1)$-orbit and the other ligand p belongs to another $\mathbf{C}_1(/\mathbf{C}_1)$-orbit. It follows that the two p's are non-equivalent to each other from the viewpoint of point groups.[66]

**$A_2p\bar{p}$-Promolecules.** The enantiospheric $\mathbf{C}_s(/\mathbf{C}_1)$-orbit shown in the right-hand side of Eq. 1 accommodates a chiral proligand (p) and its enantiomeric proligand ($\bar{p}$) in agreement with a compensated chiral packing; and each of the $\mathbf{C}_s(/\mathbf{C}_s)$-orbits (homospheric orbits) accommodates one achiral proligand of the same kind (A). Thereby, we obtain a promolecule **3** as shown in Fig. 2. The ligand packing for **3** is represented by packing (e) in Fig. 2, where the two A's are non-equivalent to each other from the viewpoint of point-group symmetries.

**2.2 Permutation-Group Symmetries.** The four positions of the tetrahedral skeleton can alternatively be regarded as being controlled by the action of the symmetric group of degree 4, which is a kind of permutation group. We use the symbol $\mathbf{S}^{[4]}$ to designate the symmetric group of degree 4, the order of which is equal to 24 as a result of the fact that the group $\mathbf{S}^{[4]}$ is isomorphic to the point group $\mathbf{T}_d$.[64] It should be noted that the 24 permutations of the CR $\mathbf{T}_d(/\mathbf{C}_{3v})$ themselves can be re-

garded as the 24 permutations of the symmetric group $\mathbf{S}^{[4]}$ if the chirality fittingness is disregarded. The subgroups of $\mathbf{S}^{[4]}$ correspond to those of $\mathbf{T}_d$, where they are numbered sequentially, i.e., $\mathbf{S}_1^{[4]}$ (= $\mathbf{C}_1$), $\mathbf{S}_2^{[4]}$, ..., and $\mathbf{S}_{11}^{[4]}$ (= $\mathbf{S}^{[4]}$). These subgroups are isomorphic to the corresponding subgroups of $\mathbf{T}_d$: i.e., $\mathbf{C}_1$ and $\mathbf{S}_1^{[4]}$ (= $\mathbf{C}_1$); $\mathbf{C}_2$ and $\mathbf{S}_2^{[4]}$; $\mathbf{C}_s$ and $\mathbf{S}_3^{[4]}$; $\mathbf{C}_3$ and $\mathbf{S}_4^{[4]}$; $\mathbf{S}_4$ and $\mathbf{S}_5^{[4]}$; $\mathbf{D}_2$ and $\mathbf{S}_6^{[4]}$; $\mathbf{C}_{2v}$ and $\mathbf{S}_7^{[4]}$; $\mathbf{C}_{3v}$ and $\mathbf{S}_8^{[4]}$; $\mathbf{D}_{2d}$ and $\mathbf{S}_9^{[4]}$; $\mathbf{T}$ and $\mathbf{S}_{10}^{[4]}$; and $\mathbf{T}_d$ and $\mathbf{S}_{11}^{[4]}$ = ($\mathbf{S}^{[4]}$).[64] The set of four positions on the action of the symmetric group $\mathbf{S}^{[4]}$ generates an orbit that is assigned to a CR $\mathbf{S}^{[4]}/\mathbf{S}_8^{[4]}$), where the global symmetry $\mathbf{S}^{[4]}$ is isomorphic to $\mathbf{T}_d$ and the local symmetry $\mathbf{S}_8^{[4]}$ is isomorphic to $\mathbf{C}_{3v}$.

The desymmetrization of the orbit is considered to generate a set of orbits, as represented by the subduction of the CR $\mathbf{S}^{[4]}/\mathbf{S}_8^{[4]}) \downarrow \mathbf{S}_i^{[4]}$ ($i$ = 1 to 11), which are illustrated by Young's tableaus of permutation. Although the form of the Young's tableau for $\mathbf{S}_i^{[4]}$ is apparently the same as that of the corresponding isomorphic subgroup of $\mathbf{T}_d$, the action of the $\mathbf{S}^{[4]}$ does not obey the chirality fittingness. Hence, it permits the packing (b) for the $ABX^2$-promolecule, the packing (d) for the $ABp^2$-promolecule, and the packing (f) for the $A^2p\bar{p}$-promolecule, which stem from the $2^11^2$-tableau of the same partition. Thus, the $ABX^2$-, $ABp^2$-, and $A^2p\bar{p}$-promolecules belong to same $\mathbf{S}_3^{[4]}$ in terms of permutation-group symmetries. As a result, the two X's in the $ABX^2$-promolecule (the packing (b)), the two p's in the $ABp^2$-promolecule (the packing (d)), and the two A's in the $A^2p\bar{p}$-promolecule (the packing (f)) are respectively equivalent under the action of $\mathbf{S}_3^{[4]}$ if we pay attention to permutation-group symmetries. As long as only achiral (pro)ligands are considered, two types of Young's tableaus are identical to each other, as found in packings (a) and (b) of Fig. 2. Once chiral (pro)ligands are taken into consideration, the two types of Young's tableaus behave differently so that Young's tableaus of permutation (e.g. (d) and (f) of Fig. 2) exhibit the "violation of chirality fittingness", while Young's tableaus of symmetry (e.g. (c) and (e) of Fig. 2) show the "observance of chirality fittingness". Thus, whereas the two p's in **2** are non-equivalent to each other from the viewpoint of point groups (see the packing (c)), they are regarded as being equivalent from the viewpoint of permutation-groups, as found in the packing (d) of Fig. 2. Young's tableau (e) from the viewpoint of point groups in Fig. 2 shows that the two A's in **3** are non-equivalent to each other and that p and $\bar{p}$ are equivalent to each other. In contrast, Young's tableau (f) from the viewpoint of permutation-groups reveals that the two A's in **3** are equivalent to each other while p and $\bar{p}$ are non-equivalent to each other. Throughout the present paper, we discuss the permutation-group and point-group symmetries of a molecule in such combined manners that promolecule **1** belongs to $\mathbf{C}_s/\mathbf{S}_3^{[4]}$; promolecule **2** belongs to $\mathbf{C}_1/\mathbf{S}_3^{[4]}$; and promolecule **3** belongs to $\mathbf{C}_s/\mathbf{S}_3^{[4]}$.

The non-equivalence of the two A's in **3** becomes clearer by examining an $AB\bar{p}p$-promolecule (**4**) as another example of the symmetry $\mathbf{C}_s$, as shown in Fig. 3. The set of proligands $ABp\bar{p}$ is placed in agreement with the $2^11^2$-tableau (Table 1), which is ascribed to the subduction $\mathbf{T}_d/\mathbf{C}_{3v}) \downarrow \mathbf{C}_s$. As a result, a pair of the proligand p and its enantiomeric proligand $\bar{p}$ occupies the enantiospheric $\mathbf{C}_s(/\mathbf{C}_1)$-orbit as a compensated chiral packing, i.e., the packing (g) shown in Fig. 3. In other words, the proligands p and $\bar{p}$ are equivalent to each other from a viewpoint of

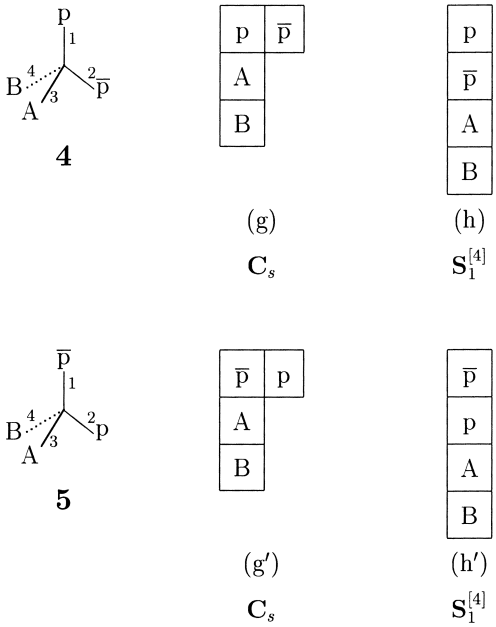



Fig. 3. Ligand packing for $ABp\bar{p}$-promolecules.

point groups. The achiral ligands A and B in **4** occupy two one-membered $\mathbf{C}_s(/\mathbf{C}_s)$-orbits in the same way as **3**.

The proligands p and $\bar{p}$ in **4** are non-equivalent to each other from the viewpoint of permuation groups. Under the permutation group $\mathbf{S}^{[4]}$, the set of ligands $ABp\bar{p}$ is placed in agreement with the $1^4$-tableau, which is derived by the subduction $\mathbf{S}^{[4]}/\mathbf{S}_8^{[4]}) \downarrow \mathbf{S}_1^{[4]}$. This results in the packing (h) shown in Fig. 3. As a result, **4** is determined to belong to $\mathbf{C}_s/\mathbf{S}_1^{[4]}$.

Figure 3 also illustrates the ligand packing for the corresponding diastereomeric $AB\bar{p}p$-promolecule (**5**). It should be noted that **4** cannot be converted into **5** on the action of any reflection operations (cf. Fig. 1). This will be discussed in terms of isomer equivalence in the next subsection.

The comparison between Figs. 2 and 3 reveals the differences between permutation and point groups in their effects on chiral ligands: (1) A chiral proligand (e.g., p) and another achiral proligand of the same kind (e.g., p) can be equivalent or non-equivalent under point groups such as $\mathbf{T}_d$, while they are always equivalent under permutation groups such as $\mathbf{S}^{[4]}$. (2) A chiral proligand (e.g., p) and its enantiomeric proligand (e.g., $\bar{p}$) can be equivalent or non-equivalent under point groups (e.g. $\mathbf{T}_d$), while they are always non-equivalent under permutation groups (e.g., $\mathbf{S}^{[4]}$).

**3 Isomer Equivalence under Point Groups and under Permutation Groups. 3.1 Stereomeric and Pseudostereomeric Relationships.** Point-group symmetries are treated by means of coset representations (CRs), where equivalence relationships under point groups are controlled by the chirality fittingness ascribed to the sphericities of the CRs. Such point-group symmetries are based on rotations (proper rotations) and rotoreflections (improper rotations) that cause no bond-breaking.[67] Although CRs are a kind of permutation representation which are related to a permutation group, their sphericities enables us to apply such permutation representations to stereochemical phenomena within the observance of chirality fittingness. Thus, a chiral ligand can change its chirality during

Table 3. Isomer Equivalence and Non-Equivalence

| | | Point-group symmetry | |
|---|---|---|---|
| | | Equivalent (stereomeric) | Non-equivalent (non-stereomeric) |
| Permutation-group symmetry | equivqlent (pseudostereomeric) | homomeric enantiomeric[a)] | diastereomeric[a)] |
| | non-equivalent (non-pseudostereomeric) | enantiomeric[b)] | diastereomeric[b)] |

a) Skeleton-based equivalence. b) Ligand-based equivalence.

the reflection processes related to such permutation representations, which are discussed by using Young's tableaus of symmetry. Promolecules or molecules contained in an equivalence class[68] due to a point group are called *stereomers*.[69] The relationship between a pair of stereomers is referred to as being *stereomeric* (Table 3).

On the other hand, permutation symmetries are considered to be based on permutations that cause bond-breaking processes.[70] This means that a chiral ligand (in isolation) does not change its chirality during such permutations, which are discussed by using Young's tableaus of permutation. Although equivalence relationships under permutation groups are controlled by the corresponding CRs (e.g. $\mathbf{S}^{[4]}(/\mathbf{S}_8^{[4]})$) and their subductions, the sphericity concept does not work for the permutation-group symmetries, in contrast to the point-group symmetries. Promolecules or molecules involved in an equivalent class under a permutation group are called *pseudostereomers*. The relationship between a pair of stereomers is referred to as being *pseudostereomeric* (Table 3).

**3.2 Isomer Symmetries as Local Symmetries in Stereoisomerism. Isomer Equivalence for $ABp_2$-Promolecules.** Figure 4 shows stereomers generated from $ABp^2$ (**2**). The twelve proper rotations of $\mathbf{T}_d$, i.e. $C_{2(1)}$ (∼ (1 2)(3 4)), $C_{2(2)}$ (∼ (1 3)(2 4)), $C_{2(3)}$ (∼ (1 4)(2 4), etc., act on **2** to generate twelve homomers, i.e., **6**, **7**, **8**, etc. (Fig. 4). On the other hand, the twelve improper rotations, i.e. $\sigma_{d(4)}$ (∼ (1 2)(3)(4)), $\sigma_{d(5)}$ (∼ (1 3)(2)(4)), $\sigma_{d(1)}$ (∼ (1) (2 3)(4)), etc., convert **2** into twelve enantiomers, **9**, **10**, **11**, etc. (Fig. 4).[71] This convertibility means that **2** and its enantiomer **9** are equivalent on the action of the point group $\mathbf{T}_d$. The twenty-four promolecules construct *an orbit of stereoisomers*, which is an equivalence class and is again contolled by a CR. The CR of this case is determined to be $\mathbf{T}_d(/\mathbf{C}_1)$. The members of such an orbit of stereoisomers are *stereomers*, as described above (Table 3). The size of the orbit is calculated to be $|\mathbf{T}_d|/|\mathbf{C}_1| = 24$. Since the $\mathbf{T}_d(/\mathbf{C}_1)$-orbit is enantiospheric, one half of the orbit is capable of accommodating the twelve homomers (**6** etc.) and the other half is capable of accommodating the same number of the corresponding enantiomers (**9** etc.). The local symmetry (stabilizer, i.e. $\mathbf{C}_1$) corresponds to the point-group symmetry of the promolecule.[72] Thus, the isomer symmetry $\mathbf{C}_1$ is regarded as a local symmetry in stereoisomerism, which is now formulated on by virtue of such a set of 24 stereomers generated on the action of $\mathbf{T}_d$. The accommodation mode of the $\mathbf{T}_d(/\mathbf{C}_1)$-orbit ($ABp^2$-homomers and the $AB\overline{p}^2$-homomers) is a compensated chiral packing for stereoisomers, which is mathematically parallel to a compensated chiral packing for ligands or proligands (Table 1).[73] The difference between the permutation symmetry and the point-group symmetry for $ABp^2$ (or $AB\overline{p}^2$) is related to Hanson's prochirality, as will be discussed later.

The permutations of the symmetric group $\mathbf{S}^{[4]}$ are classified into two categories by means of parity, i.e., even and odd permutations. On the other hand, the symmetry operations of the point group $\mathbf{T}_d$ are classified into two categories by means of

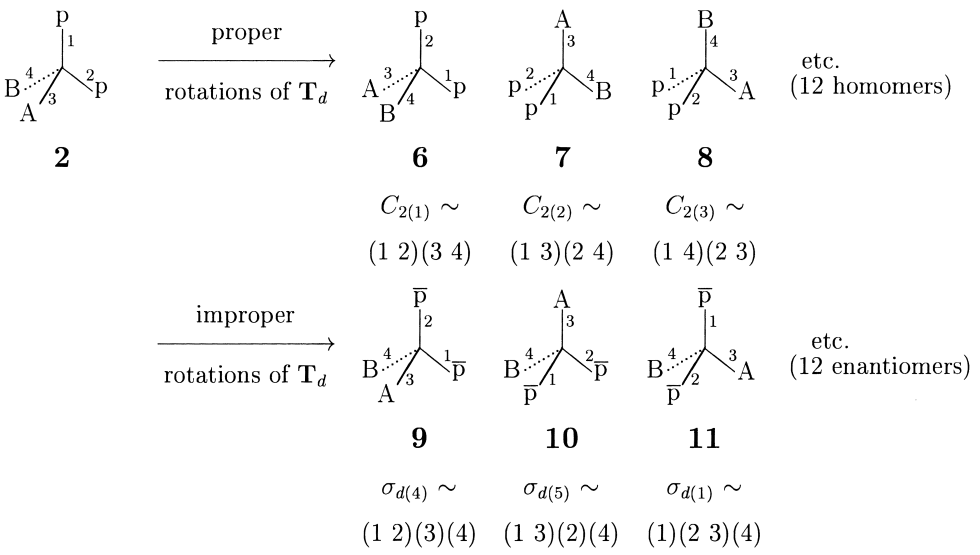



Fig. 4. Isomer equivalence for $ABp^2$ under point group $\mathbf{T}_d$.

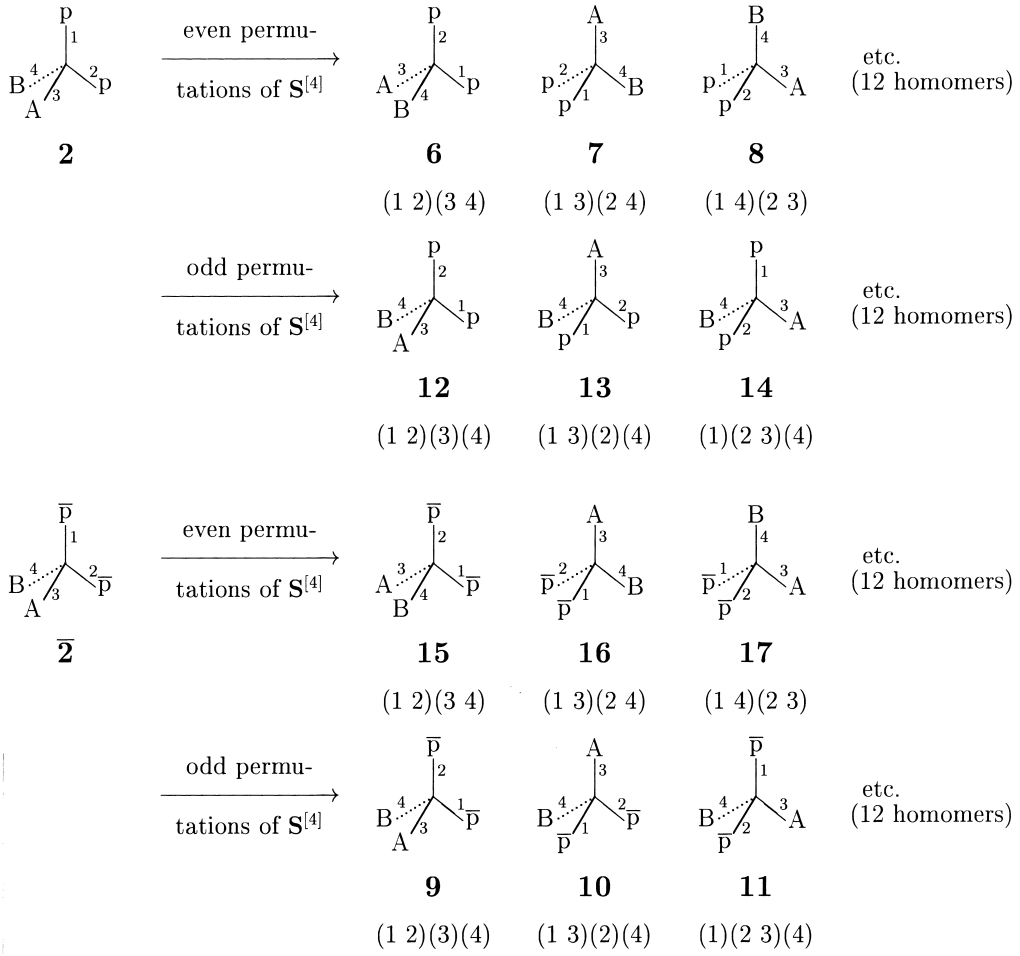



Fig. 5. Isomer equivalences for $ABp^2$ and $AB\overline{p}^2$ under permutation group $\mathbf{S}^{[4]}$.

chirality/achirality, i.e., proper and improper rotations. Since $\mathbf{S}^{[4]}$ and $\mathbf{T}_d$ are isomorphic, each of the even permutations of degree 4 corresponds to a proper rotation of the $\mathbf{T}_d$, and each of the odd permutations of degree 4 corresponds to an improper rotation of the $\mathbf{T}_d$.[75] In the present paper, the correspondence is explicity mediated by the CR $\mathbf{T}_d(/\mathbf{C}_{3v})$.[76] Although an odd permutation of $\mathbf{S}^{[4]}$ and the CR for the corresponding improper rotation have the same form, their effects on chiral (pro)ligands are different, as exemplified in Fig. 5 (cf. Fig. 4).

Each of the even permutations contained in the permutation symmetry $\mathbf{S}^{[4]}$ (Fig. 5) acts on **2** to generate one of the corresponding twelve homomers in the same manner as that of proper rotations of the poing-group symmetry $\mathbf{T}_d$. The action of the odd permutations of $\mathbf{S}^{[4]}$ ((1 2)(3)(4), (1 3)(2)(4), (1)(2 3)(4) etc.) on **2** generates another set of twelve homomers (**12**, **13**, or **14** etc.), where the ligand chiralities are not altered (Fig. 5).[77] Note that the numbering of the original skeleton (**2**) has an alternative handedness as compared with the one of the resulting skeletons (**12** etc.). The first homomer **12** is identical with **2** itself if the handedness of the numbering is ignored. In other words, **2** is fixed on the action of the permutation (1 2)(3)(4), giving a pair of homomers (**2** and **12**). This means that **2** belongs to $\mathbf{S}_3^{[4]}$ (isomorphic to $\mathbf{C}_s$) or its conjugate subgroup.[78]

Figure 5 also illustrates the action of $\mathbf{S}^{[4]}$ on $\overline{\mathbf{2}}$ (the enantiomer of **2**), where 24 homomers of $\overline{\mathbf{2}}$ are generated. Thus, the $ABp^2$ (**2**) cannot be converted into its enantiomer $AB\overline{p}^2$ ($\overline{\mathbf{2}}$) and vice versa on the action of the permutation group $\mathbf{S}^{[4]}$, although they are convertible on the action of the point group $\mathbf{T}_d$, as shown in Fig. 4. More precisely speaking, $ABp^2$ and $AB\overline{p}^2$ represent distinct isomers under $\mathbf{S}^{[4]}$ so that $ABp^2$ is assigned to a CR $\mathbf{S}^{[4]}(/\mathbf{S}_3^{[4]})$, while $AB\overline{p}^2$ is assigned to another CR of the same kind, $\mathbf{S}^{[4]}(/\mathbf{S}_3^{[4]})$.[78] In other words, the $ABp^2$ and the $AB\overline{p}^2$ differ from each other with respect to permutation symmetry. The non-equivalency between the $ABp^2$ and the $AB\overline{p}^2$ is referred to in terms of "non-pseudostereomeric" (Table 3). The inspection of the symbol $\mathbf{S}^{[4]}(/\mathbf{S}_3^{[4]})$ shows that the permutation symmetry of the $ABp^2$ (or $AB\overline{p}^2$) is $\mathbf{S}_3^{[4]}$, which is isomorphic to $\mathbf{C}_s$.

**Isomer Equivalence for ABpp̄-Promolecules.** Figure 6 shows an example for illustrating pseudostereomers, which are characterized as being contained in an equivalent class under a permutation group. The odd permutations act on ABpp̄ (**4**) to generate pseudostereomers, **18**, **19**, **20**, etc., while the even permutations generate pseudostereomers of the other category. Stereochemically speaking, each of the former pseudostereomers is diastereomeric to **4**, while each of the latter pseudostereomers is homomeric to **4**. On the oher hand, the improper rotations as well as the proper rotations of $\mathbf{T}_d$ convert the achiral promolecule **4** into homomers: **21**, **22**, **23**, etc.

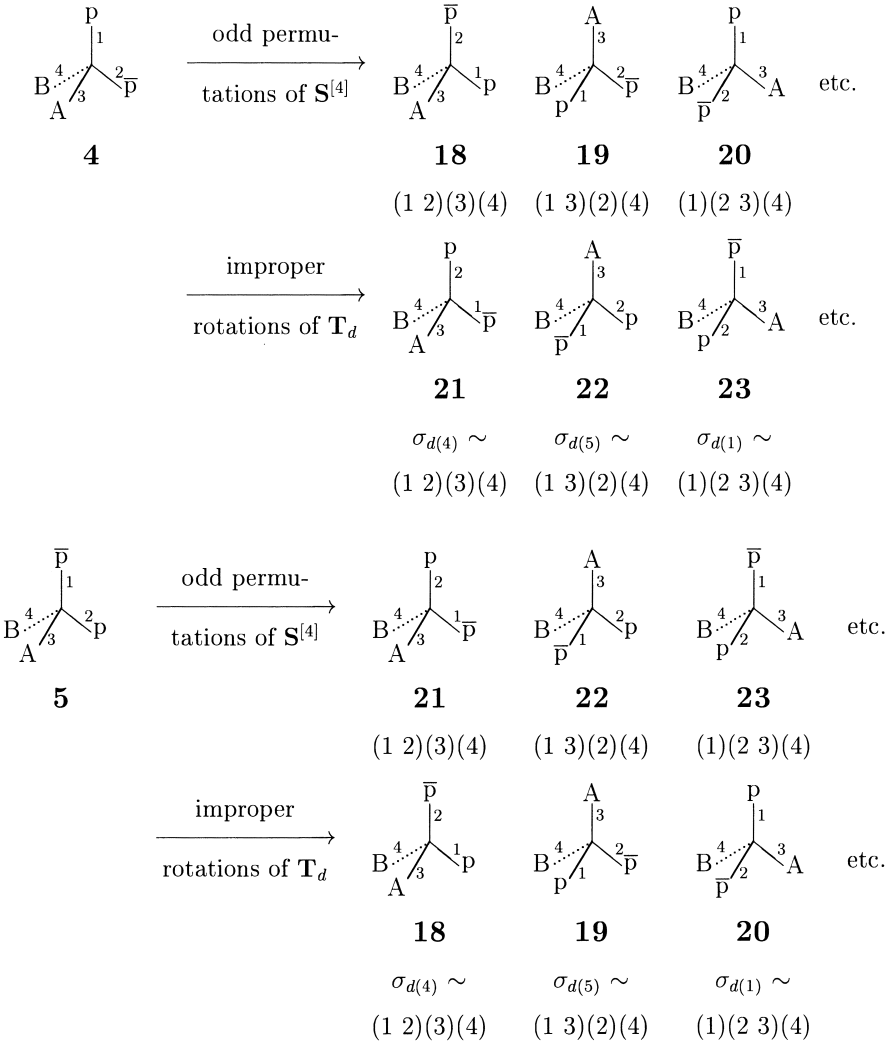


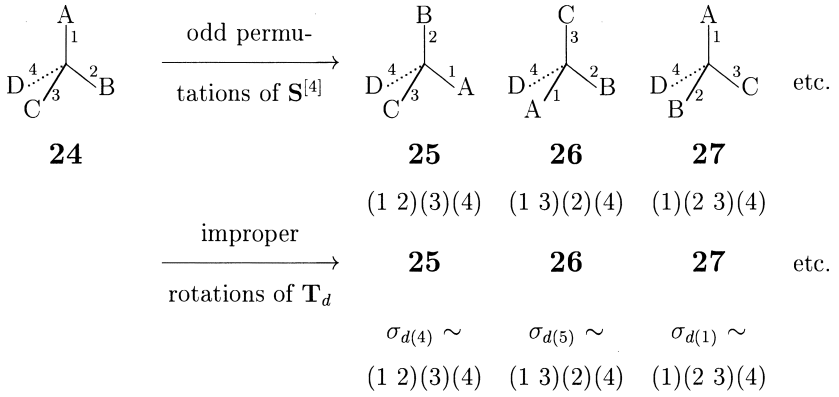

Fig. 6. Equivalence for ABp$\bar{\text{p}}$ under permutation and point groups.

The ABp$\bar{\text{p}}$ (**4**) can be converted into its pseudostereomer of the same formula AB$\bar{\text{p}}$p (**5**) on the action of the symmetric group $\mathbf{S}^{[4]}$, as shown in Fig. 6, if the numbering is disregarded.[79] Note that **5** is homomeric to the resulting **18**, which is different (diastereomeric) from **4**. More precisely speaking, **4** and **5** (or **18**), though diastereomeric, are equivalent (pseudostereomeric) under $\mathbf{S}^{[4]}$ so totally 24 pseudostereomers are assigned to the CR $\mathbf{S}^{[4]}(/\mathbf{S}_1^{[4]})$.[77,80]

In contrast, the ABp$\bar{\text{p}}$ (**4**) and the AB$\bar{\text{p}}$p (**5**) are not convertible on the action of the point group $\mathbf{T}_d$. They represent diastereomeric (non-equivalent) isomers under $\mathbf{T}_d$, so that the twelve pairs selected analogously to the set of **4** and **21** construct an orbit that is assigned to a CR $\mathbf{T}_d(/\mathbf{C}_s)$.[71] Along the same line, the twelve pairs selected analogously to the set of **5** and **18** construct another $\mathbf{T}_d(/\mathbf{C}_s)$-orbit. The local symmetry $\mathbf{C}_s$ for the CR $\mathbf{T}_d(/\mathbf{C}_s)$ corresponds to the symmetry of AB$\bar{\text{p}}$p.

**Isomer Equivalence for ABCD-Promolecules.** Figure 7 shows another example for illustrating pseudostereomers, which are characterized as being contained in an equivalent class under a permutation group but as being enantiomeric under a point group. The action of the odd permutations of $\mathbf{S}^{[4]}$ on ABCD (**24**) generates mirror images: **25**, **26**, **27**, etc., which are determined to be pseudostereomeric to the original promolecule ABCD (**24**). Stereochemically speaking, each of the pseudostereomers is enantiomeric to **24**. In this case, the improper rotations of $\mathbf{T}_d$ exhibit the same behaviors as the odd permutations so that they converts the chiral promolecule **24** into the enantiomers: i.e., **25**, **26**, **27** etc.

It should be noted that the term "pseudostereomeric" defined in the present paper partly corresponds to a conventional stereochemical term, "homomeric", "enantiomeric" or "diastereomeric" (Table 3). Stereochemically speaking, a pair of a molecule and its enantiomer is regarded as one isomer in the form of a racemic mixture under achiral conditions. On this analogy, a pair of pseudostereomers in the present permutation-group treatment is conceptually regarded as one isomer in the form of a hypothetical racemic mixture. For example, **2** and $\bar{\mathbf{2}}$ are regarded as two distinct isomers from the viewpoint of permutation-groups. They are, in turn, regarded as one isomer from the stereochemical point of view, as they are recognized to be a pair of enantiomers. From the viewpoint of permutation-groups, **4** and **18** are regarded as one isomer that is determined to give a pair of pseudostereomers. In contrast, **4** and **18** are two distinct isomers (diastereomers) from a stere-




**24** **25** **26** **27**

(1 2)(3)(4) (1 3)(2)(4) (1)(2 3)(4)

**25** **26** **27**

$\sigma_{d(4)} \sim$ $\sigma_{d(5)} \sim$ $\sigma_{d(1)} \sim$

(1 2)(3)(4) (1 3)(2)(4) (1)(2 3)(4)

Fig. 7. Equivalence for ABCD under permutation and point groups.

ochemical point of view. As for the pair of **24** and **25**, they are one isomer as a pair of pseudostereomers from the viewpoint of permutation groups and, at the same time, one isomer as a pair of enantiomers stereochemically.

**4 Promolecules under Point Groups: Observance of Chirality Fittingness.** Suppose that the four positions of a tetrahedral skeleton belonging to the point group $\mathbf{T}_d$ are occupied by a set of four ligands selected from achiral proligands:[53]

$$L_a = \{\mathrm{A}, \mathrm{B}, \mathrm{C}, \mathrm{D}\} \tag{2}$$

and chiral proligands:

$$L_c = \{\mathrm{p}, \overline{\mathrm{p}}, \mathrm{q}, \overline{\mathrm{q}}, \mathrm{r}, \overline{\mathrm{r}}, \mathrm{s}, \overline{\mathrm{s}}\}, \tag{3}$$

where the symbol with an overline represents the corresponding enantiomeric proligand.

For combinatorial enumeration, unit subduced cycle indices (USCIs)[55] and unit subduced cycle indices with chirality fittingness (USCI-CFs)[59,60] have been derived from the CRs. The latter for $\mathbf{T}_d$ are listed in the rightmost column of Table 2. The previous enumeration[54] has adopted the generating-function method based on subduced cycle indices (SCIs) among the four methods[81] of the USCI approach. In the present enumeration, we will use the generating-function method based on partial cycle indices (PCIs)[82] after the extension taking account of chirality fittingness. Therby, we obtain the partial cycle indices with chirality fittingness (PCI-CFs) as follows, by using, the data listed in Table 2 and the inverse mark table for $\mathbf{T}_d$ listed in Appendix B.1 of Ref. 56.

$$\mathrm{PCI}(\mathrm{C}_1, \$_d) = \frac{1}{24}b_1^4 - \frac{1}{8}b_2^2 - \frac{1}{4}a_1^2c_2 - \frac{1}{6}b_1b_3 + \frac{1}{12}b_4 + \frac{1}{4}a_2^2 + \frac{1}{2}a_1a_3 + \frac{1}{6}b_4 - \frac{1}{2}a_4 \tag{4}$$

$$\mathrm{PCI}(\mathbf{C}_2, \$_d) = \frac{1}{4}b_2^2 - \frac{1}{4}c_4 - \frac{1}{4}b_4 - \frac{1}{4}a_2^2 + \frac{1}{2}a_4 \tag{5}$$

$$\mathrm{PCI}(\mathbf{C}_s, \$_d) = \frac{1}{2}a_1^2c_2 - \frac{1}{2}a_2^2 - a_1a_3 + a_4 \tag{6}$$

$$\mathrm{PCI}(\mathbf{C}_3, \$_d) = \frac{1}{2}b_1b_3 - \frac{1}{2}a_1a_3 - \frac{1}{2}b_4 + \frac{1}{2}a_4 \tag{7}$$

$$\mathrm{PCI}(\mathbf{S}_4, \$_d) = \frac{1}{2}c_4 - \frac{1}{2}a_4 \tag{8}$$

$$\mathrm{PCI}(\mathbf{D}_2, \$_d) = 0 \tag{9}$$

$$\mathrm{PCI}(\mathbf{C}_{2v}, \$_d) = \frac{1}{2}a_2^2 - \frac{1}{2}a_4 \tag{10}$$

$$\mathrm{PCI}(\mathbf{C}_{3v}, \$_d) = a_1a_3 - a_4 \tag{11}$$

$$\mathrm{PCI}(\mathbf{D}_{2d}, \$_d) = 0 \tag{12}$$

$$\mathrm{PCI}(\mathbf{T}, \$_d) = \frac{1}{2}b_4 - \frac{1}{2}a_4 \tag{13}$$

$$\mathrm{PCI}(\mathbf{T}_d, \$_d) = a_4, \tag{14}$$

where the symbol \$ represents $a$, $b$, or $c$. It should be noted that $\mathrm{PCI}(\mathbf{D}_2, \$_d)$ and $\mathrm{PCI}(\mathbf{D}_{2d}, \$_d)$ are equal to zero. This means that there exist no molecules of $\mathbf{D}_{2d}$- and $\mathbf{D}_2$-symmetry in the present enumeration. Hence, this is a direct proof of the conjunction described previously.[83] In the PCI-CFs, each $a_d$ corresponds to a homospheric orbit, each $b_d$ to a hemispheric orbit, and each $c_d$ to an enantiospheric orbit. We use the following three kinds of ligand inventories:

$$a_d = A^d + B^d + C^d + D^d \tag{15}$$

$$b_d = A^d + B^d + C^d + D^d + p^d + \overline{p}^d + q^d + \overline{q}^d + r^d + \overline{r}^d + s^d + \overline{s}^d \tag{16}$$

$$c_d = A^d + B^d + C^d + D^d + 2p^{d/2}\overline{p}^{d/2} + 2q^{d/2}\overline{q}^{d/2} + 2r^{d/2}\overline{r}^{d/2} + 2s^{d/2}\overline{s}^{d/2}, \tag{17}$$

which are introduced to the PCI-CFs (4 to 14). After expansion, we have the generating functions for the respective subgroups, some of which are shown as follows:

$$f\mathbf{c}_2 = [\frac{1}{2}(A^2p^2 + A^2\bar{p}^2) + \frac{1}{2}(A^2q^2 + A^2\bar{q}^2) + \ldots] + [\frac{1}{2}(p^2q^2 + \bar{p}^2\bar{q}^2) + \frac{1}{2}(p^2r^2 + \bar{p}^2\bar{r}^2) + \ldots] \tag{18}$$

$$f\mathbf{c}_s = (A^2BC + A^2BD + \ldots) + (A^2p\overline{p} + A^2q\overline{q} + \ldots) + (2ABp\overline{p} + 2ABq\overline{q} + \ldots) \tag{19}$$

Such a term as $(1/2)(A^2p^2 + A^2\overline{p}^2)$ represents a pair of enanti-

omers so that there appears one $A^2p^2$-isomer (an enantiomeric pair). Hence, the coefficient of the term $A^2p^2$ is regarded as unity in listing such factorial data. On the other hand, such a term as $A^2p\overline{p}$ represents a so-called meso-compound, which is counted once as an isomer. Note that the term *ABCD* is used in place of (1/2)[*ABCD*(right) + *ABCD*(left)] on the basis of the model adopted in the present enumeration. The coefficients of Eqs. 18 and 19 are collected in the $\mathbf{C}_2$- and $\mathbf{C}_s$-column of Tables 4 and 5 (the "S"-row of each ligand partition). The results for the remaining subgroups are also collected in Tables 4 and 5. These results due to the PCI method are identical with those based on the subduced-cycle-index (SCI) method reported previously.[54]

**5 Promolecules under Permutation Groups: Violation of Chirality Fittingness.** In previous papers,[59,60,84] we have applied SCIs and PCIs to cases where only achiral ligands have been permitted, while we have used SCI-CFs and PCI-CFs in cases where achiral and chiral ligands are taken into consideration. In other words, such *observance of chirality fittingness* can be considered to generate *stereomers* (cf. Table 3). On the other hand, we here regard *pseudostereomers* as isomers generated by placing not only achiral but also chiral ligands *in violation of chirality fittingness*. For this purpose, we shall apply SCIs and PCIs to cases in which achiral and chiral ligands are considered on the basis of Young's tableaus of permutation. Or equivalently, we can place $a_d = b_d = c_d$ in PCI-CFs such as Eqs. 4 to 14. Note that SCI-CFs and PCI-Cfs can be transformed into SCIs and PCIs by placing $s_d = a_d = b_d = c_d$. Thus, we use the following ligand inventory for the enumeration of permutation isomers:

$$s_d = A^d + B^d + C^d + D^d + p^d + \overline{p}^d + q_d + \overline{q}^d + r^d + \overline{r}^d + s^d + \overline{s}^d. \tag{20}$$

For the sake of convenience, we place $s_\mathrm{d} = a_\mathrm{d} = b_\mathrm{d} = c_d$ in the PCI-CFs (Eqs. 4 to 14) so as to transform them into PCIs advance. Thereby, we obtain the corresponding PCIs without chirality fittingness:

$$\mathrm{PCI}(\mathbf{S}_1^{[4]}, s_d) = \frac{1}{24}s_1^4 + \frac{1}{8}s_2^2 - \frac{1}{4}s_1^2s_2 + \frac{1}{3}s_1s_3 + \frac{1}{4}s_4 \tag{21}$$

$$\mathrm{PCI}(\mathbf{S}_2^{[4]}, s_d) = 0 \tag{22}$$

$$\mathrm{PCI}(\mathbf{S}_3^{[4]}, s_d) = \frac{1}{2}s_1^2s_2 - \frac{1}{2}s_2^2 - s_1s_3 + s_4 \tag{23}$$

$$\mathrm{PCI}(\mathbf{S}_4^{[4]}, s_d) = 0 \tag{24}$$

$$\mathrm{PCI}(\mathbf{S}_5^{[4]}, s_d) = 0 \tag{25}$$

$$\mathrm{PCI}(\mathbf{S}_6^{[4]}, s_d) = 0 \tag{26}$$

$$\mathrm{PCI}(\mathbf{S}_7^{[4]}, s_d) = \frac{1}{2}s_2^2 - \frac{1}{2}s_4 \tag{27}$$

Table 4. Number of Promolecules Derived from a Tetrahedral Skeleton (Part I)

| Proligand partition | S/P | Number of promolecules | | | | | | | | | | | Remarks |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | $\mathbf{C}_1$ $\mathbf{S}_1^{[4]}$ | $\mathbf{C}_2$ $\mathbf{S}_2^{[4]}$ | $\mathbf{C}_s$ $\mathbf{S}_3^{[4]}$ | $\mathbf{C}_3$ $\mathbf{S}_4^{[4]}$ | $\mathbf{S}_4$ $\mathbf{S}_5^{[4]}$ | $\mathbf{D}_2$ $\mathbf{S}_6^{[4]}$ | $\mathbf{C}_{2v}$ $\mathbf{S}_7^{[4]}$ | $\mathbf{C}_{3v}$ $\mathbf{S}_8^{[4]}$ | $\mathbf{D}_{2d}$ $\mathbf{S}_9^{[4]}$ | $\mathbf{T}$ $\mathbf{S}_{10}^{[4]}$ | $\mathbf{T}_d$ $\mathbf{S}^{[4]}$ | |
| $A^4$ | S | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | * |
| | P | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (1) | |
| $A^3B$ | S | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | * |
| | P | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (1) | (0) | (0) | (0) | |
| $A^3p$ | S | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | §§ |
| | P | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (1) | (0) | (0) | (0) | |
| $A^2B^2$ | S | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | * |
| | P | (0) | (0) | (0) | (0) | (0) | (0) | (1) | (0) | (0) | (0) | (0) | |
| $A^2BC$ | S | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | *, ** |
| | P | (0) | (0) | (1) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | |
| $A^2Bp$ | S | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | § |
| | P | (0) | (0) | (1) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | |
| $A^2p^2$ | S | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | §§ |
| | P | (0) | (0) | (0) | (0) | (0) | (0) | (1) | (0) | (0) | (0) | (0) | |
| $A^2p\overline{p}$ | S | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | ** |
| | P | (0) | (0) | (1) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | |
| $A^2pq$ | S | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | § |
| | P | (0) | (0) | (1) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | |
| ABCD | S | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | *, ¶ |
| | P | (1) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | |
| ABCp | S | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | † |
| | P | (1) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | |
| $ABp^2$ | S | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | § |
| | P | (0) | (0) | (1) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | |
| $ABp\overline{p}$ | S | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | ‡, †† |
| | P | (1) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | |
| ABpq | S | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | † |
| | P | (1) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | |

Table 5. Number of Promolecules Derived from a Tetrahedral Skeleton (Part II)

| Proligand partition | | Number of promolecules | | | | | | | | | | | Remarks |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | $\mathbf{C}_1$ $\mathbf{S}_1^{[4]}$ | $\mathbf{C}_2$ $\mathbf{S}_2^{[4]}$ | $\mathbf{C}_s$ $\mathbf{S}_3^{[4]}$ | $\mathbf{C}_3$ $\mathbf{S}_4^{[4]}$ | $\mathbf{S}_4$ $\mathbf{S}_5^{[4]}$ | $\mathbf{D}_2$ $\mathbf{S}_6^{[4]}$ | $\mathbf{C}_{2v}$ $\mathbf{S}_7^{[4]}$ | $\mathbf{C}_{3v}$ $\mathbf{S}_8^{[4]}$ | $\mathbf{D}_{2d}$ $\mathbf{S}_9^{[4]}$ | $\mathbf{T}$ $\mathbf{S}_{10}^{[4]}$ | $\mathbf{T}_d$ $\mathbf{S}^{[4]}$ | |
| $Ap^3$ | S | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | §§ |
| | P | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (1) | (0) | (0) | (0) | |
| $Ap^2\overline{p}$ | S | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | § |
| | P | (0) | (0) | (1) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | |
| $Ap^2q$ | S | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | § |
| | P | (0) | (0) | (1) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | |
| $Ap\overline{p}q$ | S | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | † |
| | P | (1) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | |
| Apqr | S | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | † |
| | P | (1) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | |
| $p^4$ | S | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | §§ |
| | P | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (1) | |
| $p^3\overline{p}$ | S | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | §§ |
| | P | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (1) | (0) | (0) | (0) | |
| $p^3q$ | S | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | §§ |
| | P | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (1) | (0) | (0) | (0) | |
| $p^2\overline{p}^2$ | S | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | ‡ |
| | P | (0) | (0) | (0) | (0) | (0) | (0) | (1) | (0) | (0) | (0) | (0) | |
| $p^2\overline{p}q$ | S | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | § |
| | P | (0) | (0) | (1) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | |
| $p^2q^2$ | S | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | §§ |
| | P | (0) | (0) | (0) | (0) | (0) | (0) | (1) | (0) | (0) | (0) | (0) | |
| $p^2q\overline{q}$ | S | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | § |
| | P | (0) | (0) | (1) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | |
| $p^2qr$ | S | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | § |
| | P | (0) | (0) | (1) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | |
| $p\overline{p}q\overline{q}$ | S | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | ¶ |
| | P | (1) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | |
| $p\overline{p}qr$ | S | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | † |
| | P | (1) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | |
| pqrs | S | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | † |
| | P | (1) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | |

$$\mathrm{PCI}(\mathbf{S}_8^{[4]}, s_d) = s_1 s_3 - s_4 \tag{28}$$

$$\mathrm{PCI}(\mathbf{S}_9^{[4]}, s_d) = 0 \tag{29}$$

$$\mathrm{PCI}(\mathbf{S}_{10}^{[4]}, s_d) = 0 \tag{30}$$

$$\mathrm{PCI}(\mathbf{S}^{[4]}, s_d) = s_4 \tag{31}$$

As a result, we find several PCIs of zero value: $\mathrm{PCI}(\mathbf{S}_2^{[4]}, s_d)$, $\mathrm{PCI}(\mathbf{S}_4^{[4]}, s_d)$, $\mathrm{PCI}(\mathbf{S}_5^{[4]}, s_d)$, $\mathrm{PCI}(\mathbf{S}_6^{[4]}, s_d)$, $\mathrm{PCI}(\mathbf{S}_9^{[4]}, s_d)$, and $\mathrm{PCI}(\mathbf{S}_{10}^{[4]}, s_d)$. This fact means that there exist no molecules of these permutation symmetries. If we take account of achiral (pro)ligands only, this is a direct proof of the conjunction described previously.[83]

The inventory represented by Eq. 20 is introduced to the PCIs (21 to 31); then the resulting equations are expanded to give the generating functions for the respective subgroups, some of which are shown as follows:

$$\begin{aligned} f\mathbf{s}_3^{[4]} = {} & (A^2BC + A^2BD + ...) + (A^2Bp + A^2B\overline{p} + ...) \\ & + (A^2p\overline{p} + A^2q\overline{q} + ...) + (A^2pq + A^2\overline{pq} + ...) \\ & + (A^2p^2 + A^2\overline{p}^2 + ...) + (Ap^2\overline{p} + Ap\overline{p}^2 + ...) \\ & + (Ap^2q + A\overline{p}^2\overline{q} + ...) + (p^2\overline{p}q + p\overline{p}^2\overline{q} + ...) \end{aligned}$$

$$+ (p^2qr + \overline{p}^2\overline{qr} + ...) \tag{32}$$

$$\begin{aligned} f\mathbf{s}_7^{[4]} = {} & (A^2B^2 + A^2C^2 + ...) + (A^2p^2 + A^2\overline{p}^2 + ...) \\ & + (p^2\overline{p}^2 + q\overline{q}^2 + ...) + (p^2q^2 + \overline{p}^2\overline{q}^2 + ...) \end{aligned} \tag{33}$$

Since this enumeration does not take account of chirality fittingness, such terms as $A^2Bp$ and $A^2B\overline{p}$ represent distinct permutation isomers, though they are enantiomeric as stereoisomers. We select either of them, e.g. $A^2Bp$, as a representative for the sake of simplicity. These data (Eqs. 32 and 33) are collected in the $\mathbf{S}_3^{[4]}$- and $\mathbf{S}_7^{[4]}$-column of Tables 4 and 5 (the "P"-row of each ligand partition). The data for the remaining subgroups are also collected in Tables 4 and 5.

## Discussion

**1 Isomer Equivalence and the Sphericity Concept. 1.1 Enantiosphericity for Stereoisomerism.** For the purpose of specifying the sphericity concept for stereoisomerism, we first discuss the enantiosphericity for stereoisomerism. This discussion is effective to cases in which a pair of enantiomeric molecules are generated from an achiral skeleton.

We have discussed isomer equivalence for $ABp^2$ (Figs. 4 and 5) and ABCD (Fig. 7) as lower symmetry cases. In order

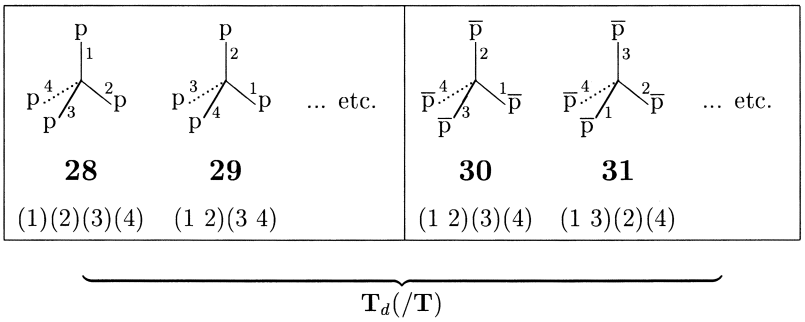



Fig. 8. Isomer equivalence for the $p^4$-promolecule under point group $\mathbf{T}_d$.

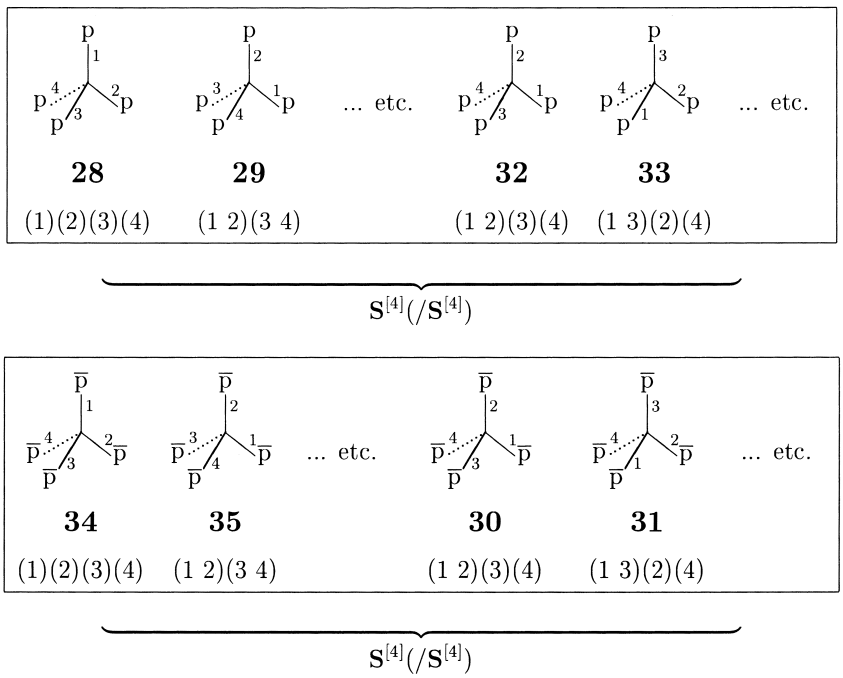



Fig. 9. Isomer equivalence for the $p^4$-promolecule under permutation group $\mathbf{S}^{[4]}$.

to illustrate isomer equivalence in general, we shall here examine other extreme cases. Figure 8 shows isomer equivalence for the $p^4$-promolecule under point group $\mathbf{T}_d$, where chirality fittingness is taken into consideration. The isomer equivalence is characterized by an orbit of stereoisomers governed by the CR $\mathbf{T}_d(/\mathbf{T})$. Thus the twelve proper rotations of $\mathbf{T}_d$ act on the four positions of a tetrahedral skeleton to generate twelve homomers, which construct one half of the two-membered $\mathbf{T}_d(/\mathbf{T})$-orbit, while the twelve improper rotations of $\mathbf{T}_d$ generate twelve enantiomers of the same kind, which construct the other half of the two-membered $\mathbf{T}_d(/\mathbf{T})$-orbit. Since the $\mathbf{T}_d(/\mathbf{T})$-orbit is enantiospheric, this packing is concluded to be a compensated chiral packing for isomers. This indicates that objects for the chirality-fittingness column in Table 1 can be promolecules or molecules. The local symmetry **T** represents the point-group symmetry of the isomer. In general, *an enantiomeric relationship is ascribed to the enantiospheric orbit of stereoisomers*.

As exemplified in the preceding paragraph, the chirality fittingness derived from the sphericity concept (Table 1) enables us to discuss global symmetries (e.g. stereoisomerism) and local symmetries (e.g. stereochemistry in a molecule) on a common basis. Hence, the Mislow–Siegel discussion based on "stereochemistry without stereoisomerism"[31] is now concluded to overestimate local symmetries (stereochemistry in a molecule). The sphericity concept of the present approach gives a foundation for discussing stereochemistry as well as stereoisomerism.

Figure 9 shows isomer equivalence for the $p^4$-promolecule under the symmetric group $\mathbf{S}^{[4]}$, which is isomorphic to $\mathbf{T}_d$. The twelve even permutations as well as the twelve odd permutations on **28** generate 24 pseudostereomers, though these are homomeric in this case. The 24 pseudostereomers are considered to be one isomer, which is ascribed to a one-membered $\mathbf{S}^{[4]}(/\mathbf{S}^{[4]})$-orbit. The corresponding enantiomer **34** is converted into 24 pseudostereomers, which are ascribed to the other one-membered $\mathbf{S}^{[4]}(/\mathbf{S}^{[4]})$-orbit. It follows that the enantiomeric relationship between **28** and **34** cannot be treated by the permutation-group symmetry.

**1.2 Homosphericity and Hemisphericity for Stereoisomerism.** We next discuss the homosphericity for stereoisomerism. This is effective for cases in which an achiral molecule is

generated from an achiral skeleton. We have discussed isomer equivalence for ABp$\bar{\text{p}}$ (Fig. 6), where the stereoisomerism is explained by the CR $\mathbf{T}_d(/\mathbf{C}_s)$. Since the CR $\mathbf{T}_d(/\mathbf{C}_s)$ is homospheric (Table 1), the homosphericity for the stereoisomerism is concluded to be concerned with homomers. Thus, we obtain a proposition that *a homomeric relationship is ascribed to the homospheric orbit of stereoisomers*.

For the purpose of examining the generality of this proposition, we shall examine a further case of higher symmetry (Fig. 12). The ligand set $A^2B^2$ is placed on the tetrahedral skeleton to give a promolecule **44**. The action of the proper and improper rotations of $\mathbf{T}_d$ gives 24 homomers, as shown in Fig. 12. From these homomers, **44** itself (by $I \sim$ (1)(2)(3)(4)), **45** (by $C_{2(1)} \sim$ (1 2)(3 4), **48** (by $\sigma_{d(4)} \sim$ (1 2)(3)(4)), and **49** (by $\sigma_{d(2)} \sim$ (1)(2)(3 4)) are identical with each other if the numbering of positions is ignored. Hence, **44** is concluded to belong to the point group $\mathbf{C}_{2v}$ (= $\{I, C_{2(1)}, \sigma_{d(4)}, \sigma_{d(2)}\}$). The stereoisomerism in this case is explained by the CR $\mathbf{T}_d(/\mathbf{C}_{2v})$. Since the CR $\mathbf{T}_d(/\mathbf{C}_{2v})$ is homospheric, the homosphericity for the stereoisomerism is concluded to be concerned with homomers.

If we presume, on the other hand, that a chiral molecule is generated from a chiral skeleton, it can be related to chiral homomers but cannot be related to the corresponding enantiomer under the point-group symmetry of the chiral skeleton. Hence, we arrive at a proposition that *the other homomeric relationship is ascribed to the hemispheric orbit of stereoisomers*.

It should be emphasized here that the sphericity concept is effective to specify stereochemistry in a molecule and stereoisomerism among molecules. Stereochemically speaking, a hemispheric orbit in a chiral molecule can be related to a hemispheric orbit of opposite chirality, which is contained in the enantiomer of the chiral molecule. From the viewpoint of stereoisomerism, on the other hand, a hemispheric orbit that contains chiral molecules derived from a chiral skeleton can be related to a hemispheric orbit of opposite chirality, which is based on the corresponding enantiomeric skeleton.

## 2 Skeleton-Based and Ligand-Based Stereoisomerism.

**2.1 Two Kinds of Enantiomers under Permutation-Group Symmetry.** Enantiomers are a kind of stereomers, which belong to an equivalence class (i.e. an enantiospheric orbit) from the viewpoint of point-group symmetry. There emerge two kinds of enantiomers if we take account of permutation-group symmetry. Thus, we can classify them into *skeleton-based enantiomers* and *ligand-based enantiomers* (Table 3).

Skeleton-based enantiomers are defined as being enantiomeric and pseudostereomeric to each other (Table 3). The skeleton-based enantiomers are illustrated by the enantiomeric pair of **24** and **25** (ABCD), which is pseudostereomeric, as shown in Fig. 7. The enumeration results P and S (¶ in Table 4) are equal, in accord with the rationalization described in Fig. 7.

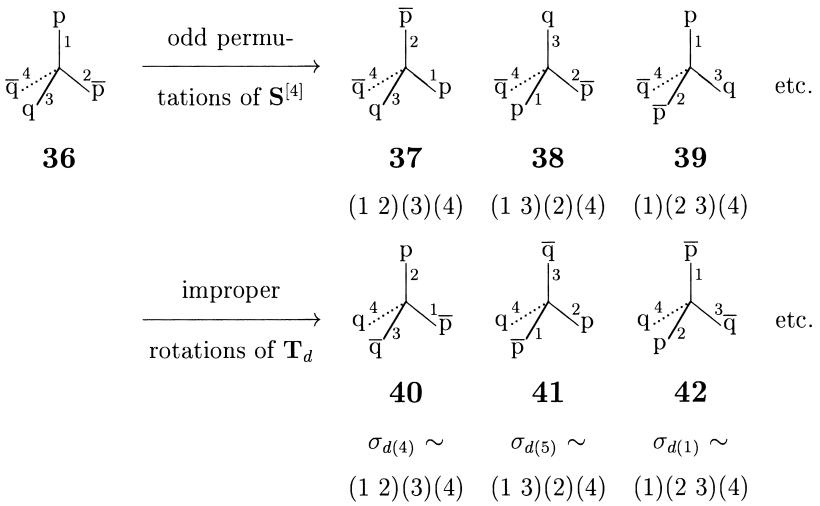
The inspection of Table 5 (¶) indicates another example of a skeleton-based enantiomeric pair (p$\bar{\text{p}}$q$\bar{\text{q}}$), which gives parallel enumeration results for P (permutation-group symmetry) and for S (point-group symmetry). The conversions of p$\bar{\text{p}}$q$\bar{\text{q}}$ are depicted in Fig. 10. Thus, the odd permutations of $\mathbf{S}^{[4]}$ convert **36** into enantiomers (**37** etc.); and the improper rotations of $\mathbf{T}_d$ convert **36** into enantiomers (**40** etc.). Although the conversions are complicated because of ligand chirality changes, the features of skeleton-based enantiomers are found by the comparison of Fig. 10 with Fig. 7.

Ligand-based enantiomers are defined as being enantiomeric but non-pseudostereomeric to each other (Table 3). The ligand-based enantiomers are illustrated by the enantiomeric pair of **2** and $\bar{2}$ (ABp$^2$), which is non-pseudostereomeric, as shown in Fig. 5. The enumeration results P and S (§ in Table 4) are different in accord with the rationalization described in Fig. 5.

The inspection of Tables 4 and 5 indicates other examples of ligand-based enantiomeric pairs, which are designated by the symbols § and §§. The two types of enumerations for each case (with respect to point-group symmetry and permutation-point symmetry) give different results, as found in the S row and the P row.

The examples with the symbol § have Young's tableaus of symmetry different from their Young's tableaus of permutation, as shown for ABp$^2$ in Fig. 2c and 2d.

For the examples with the symbol §§, on the other hand, Young's tableaus of symmetry are apparently the same as




**36** **37** **38** **39**

(1 2)(3)(4) (1 3)(2)(4) (1)(2 3)(4)

**40** **41** **42**

$\sigma_{d(4)} \sim$ (1 2)(3)(4) $\sigma_{d(5)} \sim$ (1 3)(2)(4) $\sigma_{d(1)} \sim$ (1)(2 3)(4)

Fig. 10. Equivalence for p$\bar{\text{p}}$q$\bar{\text{q}}$ under permutation and point groups.

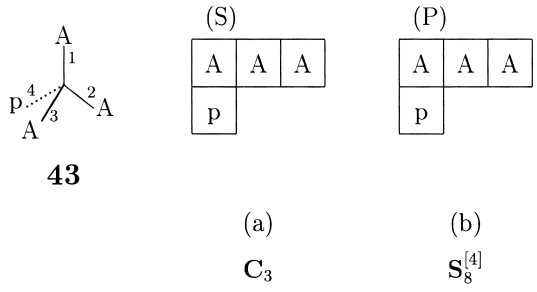



Fig. 11. Ligand packing for $A^3p$-promolecules.

Young's tableaus of permutation. However, the chirality fittingness differentiates between the two types of tableaus. Figure 11 shows the two types of tableaus for the $A^3p$-promolecule. The $A^3p$-promolecule (**43**) belongs to $\mathbf{C}_3$ stereochemically and to $\mathbf{S}_8^{[4]}$ (isomorphic to $\mathbf{C}_{3v}$) in the light of permutation groups. The packing for $\mathbf{C}_{3v}$ (Table 2) is forbidden according to the chirality fittingness, since the homospheric $\mathbf{C}_{3v}(/\mathbf{C}_{3v})$-orbit cannot accommodate a chiral proligand p. Hence, the packing (a) for $\mathbf{C}_3$ (Fig. 11) is allowed after the homospheric orbit is desymmetrized into a hemispheric $\mathbf{C}_3(/\mathbf{C}_3)$-orbit. From the viewpoint of permutation-group symmetry, the $\mathbf{S}_8^{[4]}(/\mathbf{S}_8^{[4]})$-orbit is capable of accommodating the chiral proligand p. Hence, the $A^3p$-molecule is characterized by the symbol $\mathbf{C}_3/\mathbf{S}_8^{[4]}$. As similar promolecules, we can select $p^4$ ($\mathbf{T}/\mathbf{S}^{[4]}$), $A^3p$ ($\mathbf{C}_3/\mathbf{S}_8^{[4]}$), $A^2p^2$ ($\mathbf{C}^2/\mathbf{S}_7^{[4]}$), $Ap^3$ ($\mathbf{C}_3/\mathbf{S}_8^{[4]}$), etc. from Tables 4 and 5.

**2.2 Two Kinds of Diastereomers under Permutation-Group Symmetry.** Diastereomers are one category of non-stereomers, each of which belongs to a distinct equivalence class from the viewpoint of point-group symmetry. If we take account of permutation-group symmetry, we have *skeleton-based diastereomers* and *ligand-based diastereomers* (Table 3).

Skeleton-based diastereomers are defined as being non-stereomeric but pseudostereomeric to each other (Table 3). For example, Fig. 6 has shown that ABpp̄ (**4**) and ABp̄p (**5** or **18**), though diastereomeric (i.e. non-stereomeric under $\mathbf{T}_d$), are equivalent (pseudostereomeric) under $\mathbf{S}^{[4]}$. As found easily, Tables 4 and 5 indicate that ABCp, ABpp̄, ABpq, Appq̄, Apqr, p̄qr, and pqrs have skeleton-based diastereomers, because the enumeration in each row contains two isomers (or more in general).

Ligand-based diastereomers are defined as being non-stereomeric and non-pseudostereomeric to each other (Table 3). Since the enantiomeric pair of ligands p and p̄ have the same molecular formula, $A^2p^2$ and $A^2p\bar{p}$ listed in Table 4 are concluded to be ligand-based diastereomers. Such a set as $A^2p^2$ and $A^2p\bar{p}$ is called a ligand set for a set of ligand-based diastereomers. From the data listed in Tables 4 and 5, we obtain ligand sets for ligand-based diastereomers, as collected in Table 6, where the ligand sets in each pair of brackets give the same enumeration results as the preceding ligand set does. The latter has been shown in the corresponding row of Table 4 or 5. Ligand sets with an asterisk correspond to skeleton-based diastereomers as well as to ligand-based ones.

It should be noted here that the present discussion takes no account of cases in which two chiral ligands (e.g. p and q) are diastereomeric. This type of isomerism provides another type of diastereomers, which remain open to further investigation.

**3 Permutational Aspects for the Stereogenicity of the CIP System.** There are several examples in which both skeleton-based and ligand-based enantiomerisms work, as designated by the symbol † in Tables 4 and 5. The examination of these examples provides us with permutational aspects of the CIP system.

From the viewoint of the present permutation-group symmetry, the CIP system is regarded as being based on the numbering of a promolecule of $\mathbf{S}_1^{[4]}$-symmetry (isomorphic to $\mathbf{C}_1$), the enumeration result of which is listed in each of the P rows of Tables 4 and 5. From the data listed in Tables 4 and 5, the CIP system deals with ABCD, ABCp, ABpp̄, ABpq, Appq̄, Apqr, pp̄qq̄, pp̄qr, and pqrs as examples of this type of molecule. In other words, the stereogenicity of tetrahedral molecules is ascribed to the $\mathbf{S}_1^{[4]}$-symmetry, which is the lowest subgroup (the identity group) of the symmetric group $\mathbf{S}^{[4]}$. These

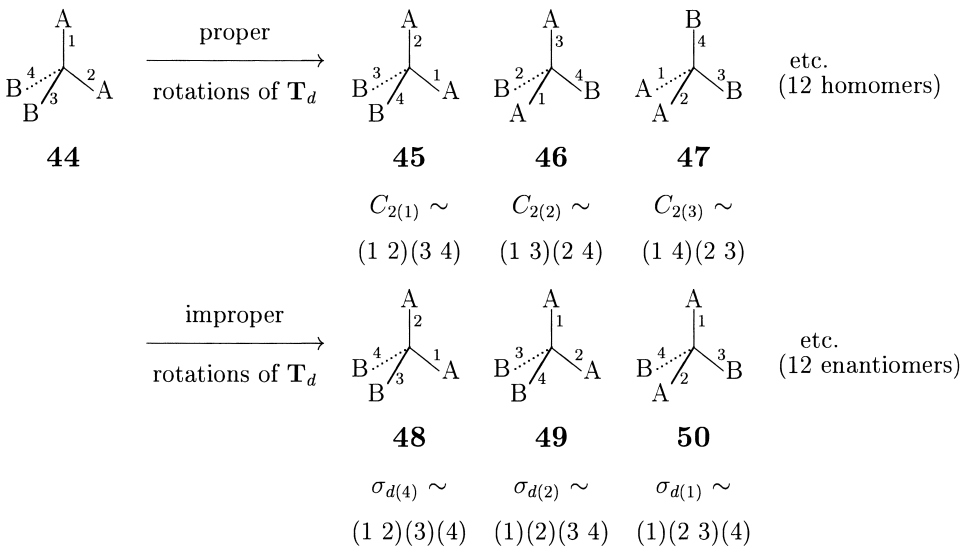
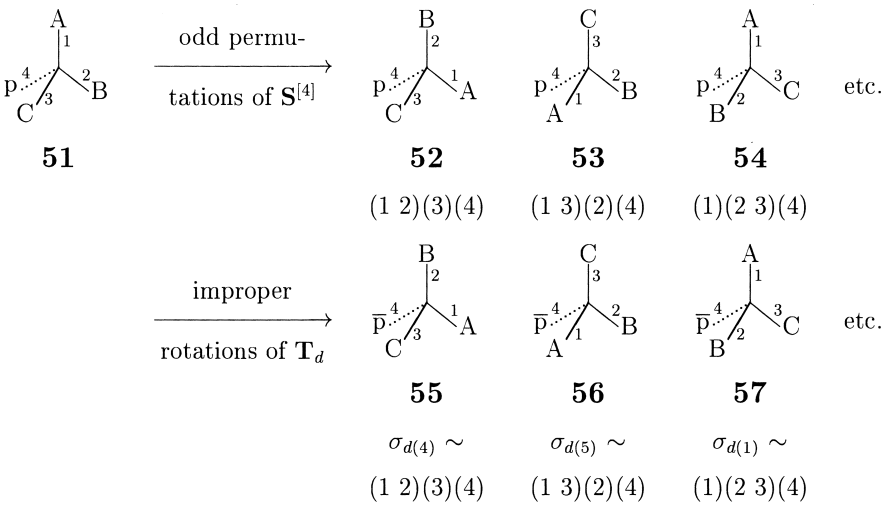



Fig. 12. Isomer equivalence for $A^2B^2$ under point group $\mathbf{T}_d$.

Table 6. Ligand Sets for Ligand-Based Diastereomers

| Achiral and chiral ligands | Chiral ligands only |
|---|---|
| $A^2p^2$, $A^2p\bar{p}$ | $p^4$, $p^3\bar{p}$, $p^2\bar{p}^2$, |
| $A^2pq$ [$A^2\bar{p}q$] | $p^3q$ [$p^3\bar{q}$], $p^2\bar{p}q$ [$p^2\bar{p}\bar{q}$] |
| $ABp^2$, $ABp\bar{p}$* | $p^2q^2$ [$p^2\bar{q}^2$], $p^2q\bar{q}$ [$p\bar{p}q^2$], $p\bar{p}q\bar{q}$ |
| $ABpq$* [$AB\bar{p}q$] | $p^2qr$ [$p^2\bar{q}r$, $p^2q\bar{r}$, $p^2\bar{q}\bar{r}$], $p\bar{p}qr$* [$p\bar{p}\bar{q}r$] |
| $Ap^3$, $Ap^2\bar{p}$ | $pqrs$* [$\bar{p}qrs$, $p\bar{q}rs$, $pq\bar{r}s$, $pqr\bar{s}$, $\bar{p}\bar{p}rs$, $p\bar{q}\bar{q}rs$ $p\bar{q}r\bar{s}$, $pq\bar{r}\bar{s}$] |
| $Ap^2q$ [$Ap^2\bar{q}$], $Ap\bar{p}q$* | |
| $Apqr$* [$Ap\bar{q}r$, $Apq\bar{r}$] | |




**51** **52** **53** **54**

(1 2)(3)(4) (1 3)(2)(4) (1)(2 3)(4)

**55** **56** **57**

$\sigma_{d(4)} \sim$ (1 2)(3)(4) $\sigma_{d(5)} \sim$ (1 3)(2)(4) $\sigma_{d(1)} \sim$ (1)(2 3)(4)

Fig. 13. Isomer equivalence of ABCp under permutation and point groups.

promolecules are classified into three categories: (a) $\mathbf{C}_1/\mathbf{S}_1^{[4]}$-type I such as ABCD and $p\bar{p}q\bar{q}$ designated by the symbol ¶; (b) $\mathbf{C}_1/\mathbf{S}_1^{[4]}$-type II such as ABCp, ABpq, $Ap\bar{p}q$, Apqr, $p\bar{p}qr$, and pqrs designated by the symbol†; and (c) $\mathbf{C}_s/\mathbf{S}_1^{[4]}$ such as $ABp\bar{p}$ designated by the symbol ††. According to this classification, the stereogenicity of tetrahedral molecules is concluded to contain three cases, which have provided the terminology of stereogenicity with some complicated features. The simplified and straightforward nature of the present treatment should be emphasized again: *The stereogenicity of tetrahedral molecules is ascribed to the* $\mathbf{S}_1^{[4]}$*-symmetry under the action of the symmetric group* $\mathbf{S}^{[4]}$.

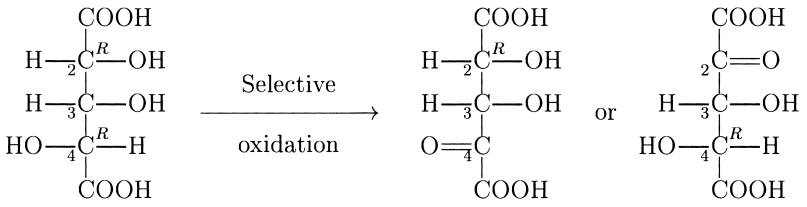
Among the three categories, the $\mathbf{C}_1/\mathbf{S}_1^{[4]}$-type I promolecules (ABCD and $p\bar{p}q\bar{q}$), both of which are chiral, have been discussed in terms of skeleton-based enantiomerism. The number (1) listed in the ABCD (P)-row of Table 4 corresponds to a pair of enantiomers. The action of an improper rotation also generates a pair of enantiomers. The number (1) listed in the ABCD (S)-row of Table 4 corresponds to one pair of such enantiomers. Thus, in general, a promolecule of $\mathbf{C}_1/\mathbf{S}_1^{[4]}$-type I generates one pair of such enantiomers. The two promolecules of $\mathbf{C}_1/\mathbf{S}_1^{[4]}$-type I (i.e. ABCD and $p\bar{p}q\bar{q}$.) are the only examples where the R and S symbols of the CIP system are concerned with enantiomerism.

Let us examine the ABCp-promolecule (**51**) shown in Fig. 13 in order to clarify the properties of $\mathbf{C}_1/\mathbf{S}_1^{[4]}$-type II promolecules. A permutation of odd parity acts on **51** to generate a pseudostereomer (diastereomer) such as **52**. The number (1) listed in the ABCp (P)-row of Table 4 corresponds to a pair of the diastereomers. On the other hand, the action of an improper rotation generates an enantiomer such as **55**. The number (2) listed in the ABCp (S)-row of Table 4 corresponds to two diastereomeric pairs of such enantiomers, where **51** and **52** are non-equivalent (non-stereomeric) under point-group symmetry. Thus, in general, a promolecule of $\mathbf{C}_1/\mathbf{S}_1^{[4]}$-type II generates two diastereomeric pairs of such enantiomers.

The CIP system compares the ABCp-promolecule (**51**) with its diastereomeric ACBp-promolecule (e.g. **52**) in the process of numbering ligands. Strictly speaking, the ABCp-promolecule (**51**) should be compared with and its enantiomer $ACB\bar{p}$-promolecule (e.g. **55**) in place of its diastereomeric ACBp-promolecule (e.g. **52**). It follows that that the R and S symbols of the CIP system are concerned with diastereoisomerism in characterizing promolecules of $\mathbf{C}_1/\mathbf{S}_1^{[4]}$-type II.

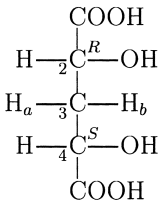
The two $ABp\bar{p}$-promolecules ($\mathbf{C}_s/\mathbf{S}_1^{[4]}$) are achiral as found in Fig. 6, where the R and S symbols of the CIP system are concerned with diastereomerism. As designated by the symbol †† in Tables 4 and 5, these promolecules are only examples of $\mathbf{C}_s/\mathbf{S}_1^{[4]}$.

**4 Permutational Aspects for the Prostereogenicity of the CIP System.** As found in the enumeration result listed in each of the P rows of Tables 4 and 5, the prostereogenicity of the CIP System (and equivalently Hanson's prochirality) is regarded as being based on the numbering of a promolecule of $\mathbf{S}_3^{[4]}$-symmetry, i.e., $A^2BC$, $A^2Bp$, $A^2p\bar{p}$ $A^2pq$, $ABp^2$, $Ap^2\bar{p}$, $Ap^2q$, $p^2\bar{p}q$, $p^2q\bar{q}$, or $p^2qr$. They are classified into two categories: (a) $\mathbf{C}_s/\mathbf{S}_3^{[4]}$ such as $A^2BC$ and $A^2p\bar{p}$ designated by the symbol **; and (b) $\mathbf{C}_1/\mathbf{S}_3^{[4]}$ such as $A^2Bp$, $A^2pq$, $ABp^2$, $Ap^2\bar{p}$, $Ap^2q$,




**58** **59** **60**

Fig. 14. Hypothetical reaction of chiral 2, 3, 4-trihydroxyglutaric acid.



**61**

Fig. 15. Meso-2, 4-dihydroxyglutaric acid.

$p^2\bar{p}q$, $p^2q\bar{q}$, and $p^2qr$ designated by the symbol §. The present treatment is capable of *ascribing the prostereogenicity of tetrahedral molecules to the* $\mathbf{S}_3^{[4]}$*-symmetry under the action of the symmetric group* $\mathbf{S}^{[4]}$.

The $\mathbf{C}_s/\mathbf{S}_3^{[4]}$ cases (** in Tables 4 and 5) have been discussed in Fig. 2. Note again that the two A's in $A^2BC$ (or the two X's in $ABX^2$) belong to a two-membered enantiospheric orbit ($\mathbf{C}_s$(/$\mathbf{C}_1$)), while A and B distinctly belong to a one-membered homospheric orbit ($\mathbf{C}_s$(/$\mathbf{C}_s$)). Since the equivalence of the two A's becomes disturbed under external chiral conditions, the four ligands in $A^2BC$ can be sequentially numbered.

On the other hand, each of the two A's in $A^2p\bar{p}$ distinctly belongs to a one-membered homospheric orbit ($\mathbf{C}_s$(/$\mathbf{C}_s$)), while p and $\bar{p}$ in $A^2p\bar{p}$ belong to a two-membered enantiospheric orbit ($\mathbf{C}_s$(/$\mathbf{C}_1$)). Since the equivalence of p and $\bar{p}$ becomes disturbed under external chiral conditions but the two A's are inherently non-equivalent under point-group symmetry, the four ligands in $A^2p\bar{p}$ can be sequentially numbered. It should be noted that the differentiation between the two A's of $A^2p\bar{p}$ requires no external chiral conditions, because each of them belongs to a one-membered homospheric orbit ($\mathbf{C}_s$(/$\mathbf{C}_s$)) and that the p and $\bar{p}$ of $A^2p\bar{p}$ cannot be differentiated under achiral conditions.

The $ABp^2$-promolecule (§ in Tables 4 and 5) has been discussed as an example of $\mathbf{C}_1/\mathbf{S}_3^{[4]}$ (Fig. 5). Note again that the two p's in $ABp^2$ are non-equivalent under point-group symmetry. Since the four ligands in $ABp^2$ are non-equivalent under point-group symmetry, they can be sequentially numbered.

For example, the two carboxyhydroxymethyl ligands (*R*-CH(OH)COOH) of 2,3,4-trihydroxyglutaric acid (**58**) are assigned to the proligands p of the $ABp^2$-promolecule. Although the *R*-CH(OH)COOH at 2-position is designated to be *pro-S* and the *R*-CH(OH)COOH at 4-position is designated to be *pro-R*, each of them distinctly belongs to a one-membered $\mathbf{C}_1$(/$\mathbf{C}_1$)-orbit. Either one of these ligands can be selectively oxidized so as to give **59** or **60** (Fig. 14), where no chiral condition is required other than its own chirality.

**5 Prochirality for Stereochemistry.** Prochirality adopted in the present paper is based on IUPAC Rule E-4.12(a)[15] after redefinition by the sphericity concept: A promolecule or molecule that has at least one enantiospheric orbit of objects (atoms, ligands or proligands) is defined as being prochiral. Although the essential features of the prochirality have been discussed in a previous paper,[34] we shall here mention several comments that are derived from the comparison between point-group symmetries and permutation-group ones.

As a prochiral promolecule in the present sense, **3** shown in Fig. 2 is reexamined here. The ligand packing for **3**, represented by packing (e) in Fig. 2, shows that the p and the $\bar{p}$ are equivalent so as to belong to a two-membered enantiospheric orbit ($\mathbf{C}_s$(/$\mathbf{C}_1$)). The prochirality of **3** is ascribed to the enantiosphericity of the $\mathbf{C}_s$(/$\mathbf{C}_1$)-orbit (p and $\bar{p}$). Compare the packing (e) and the packing (a) in Fig. 2 under the consideration of chirality fittingness. It should be noted that the two A's of **3** are non-equivalent, since they belong distinctly to one-membered $\mathbf{C}_s$(/$\mathbf{C}_s$)-orbits.

Hanson's prochirality (IUPAC Rule E-4.12(b)[15] or the prostereogenicity of the CIP system) is ascribed to the two A's of **3**, as shown by the packing (f) in Fig. 2 under permutation-group symmetry. This should be compared with the packing (b) in Fig. 2 under permutation-group symmetry. Let us examine meso-2,4-dihydroxyglutaric acid (**61**) as an example of the promolecule **3** (Fig. 15). The hydrogens $H_a$ and $H_b$ on the central carbon of **61** are designated by the symbol *pro-s* and *pro-r* respectively by means of Hanson's criteria.[6] Although this differentiation is useful, it should be noted that $H_a$ and $H_b$ can be differentiated chemically (*without any external chiral conditions*) to generate two diastereomeric products. On the other hand, a chiral condition can distinguish two chiral ligands, *R*-CH(OH)COOH and *S*-CH(OH)COOH, to generate either of two enantiomeric (chiral) products. These conclusions are directly from the Young's tableaus (e) shown in FIg. 2.

The $p^2\bar{p}^2$-promolecule ascribed to the $\mathbf{S}^4/\mathbf{S}_7^{[4]}$-symmetry (**62**) is a special case, in which the point-group and the permutation group approaches give different tableaus with different modes of packing (Fig. 16). The packing (a) of Fig. 16 is in accord with the chirality fittingness, since the enantiospheric $\mathbf{S}_4$(/$\mathbf{C}_1$)-orbit can accommodate two p's and two $\bar{p}$'s in agreement with a compensated chiral packing. McCasland synthesized several examples of this type of molecule.[85,86]

From the viewpoint of permutation groups, however, the two p's occupy one $\mathbf{S}_7^{[4]}$(/$\mathbf{S}_3^{[4]}$)-orbit, while the two $\bar{p}$'s occupy the other $\mathbf{S}_7^{[4]}$(/$\mathbf{S}_3^{[4]}$)-orbit, as found in the packing (b) of Fig. 16.

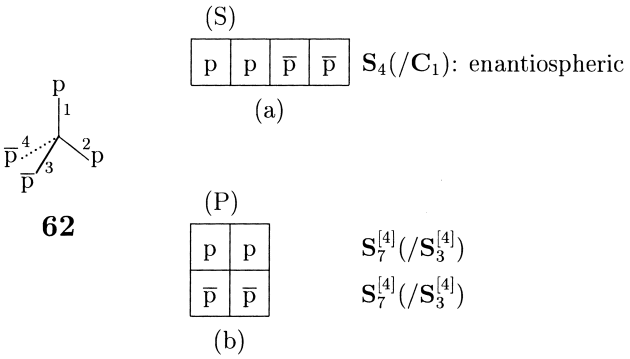



Fig. 16. Ligand partitions for $p^2\bar{p}^2$ under point-group symmetry and under permutation-group symmetry.

Since the corresponding orbit $\mathbf{C}_{2v}(/\mathbf{C}_s)$ for $\mathbf{C}_{2v}$ is homospheric, stereochemically speaking, such a packing as (b) (Fig. 16) is in violation of the chirality fittingness.

The differentiation between the two p's or between the two $\bar{p}$'s is unnecessary to depict the structure of the promolecule. It follows that Hanson's rule or the CIP rule is not required to characterize it. In spite of this fact, **62** is concluded to be prochiral because of the enantiospheric $\mathbf{S}_4(/\mathbf{C}_1)$-orbit. This example again indicates that the sequential rule by Hanson's prochirality or the prostereogenicity of the CIP system is not always related to the prochirality of the present definition.

**6 Prochirality for Stereoisomerism.** The prochirality for stereoisomerism among molecules can be defined by the enantiosphericity of an orbit on the same line as the prochirality for a molecule. The present approach shows that a chiral promolecule ($\mathbf{G}_i$) derived from an achiral skeleton of the symmetry $\mathbf{G}$ is assigned to a CR represented by $\mathbf{G}(/\mathbf{G}_i)$. The chiral promolecule and its homomers are contained in one half of the $\mathbf{G}(/\mathbf{G}_i)$-orbit, while its enantiomers are contained in the other half of the $\mathbf{G}(/\mathbf{G}_i)$-orbit. In other words, the two halves construct a racemic mixture. See the $\mathbf{T}_d(/\mathbf{T})$ case illustrated in Fig. 8. As known well in stereochemistry, such a racemic mixture can be optically resolved to produce each of the enantiomers. This process is concerned with the differentiation between enantiomers and can be referred to as the prochirality for stereoisomerism. Note that this terminology is parallel to the prochirality of a molecule which is concerned with the differentiation between enantiotopes.[87] It should be emphasized that both of the terms, *enantiomers and enantiotopes*, are commonly based on the enantiosphericity. Thereby, stereoisomerism among molecules and stereochemistry in a molecule can be discussed on a common basis.

## Conclusion

Promolecules based on a tetrahedral skeleton have been analyzed by the comparison between a permutation-group approach and a point-group one. Young's tableaus of symmetry and those of permutation have been used for characterizing the ways of ligand packing. The process for deriving the promolecules under permutation groups has been formulated as the violation of chirality fittingness. On the other hand, the process for deriving the promolecules under point groups has been formulated as the observation of chirality fittingness, which has been discussed by the sphericity concept. Stereochemistry in a tetrahedral molecule and stereoisomerism among tetrahedral molecules have been investigated on a common basis by applying the sphericity concept to the global symmetries and local symmetries of promolecules, where the global symmetries of promolecules have been specified as the "local symmetries of stereoisomerism". Thus, the stereoisomerism is discussed by virtue of orbits of stereoisomers that are governed by coset representations. Thereby, a homomeric relationship is ascribed to the homospheric orbit of stereoisomers or to the hemispheric orbit of stereoisomers; an enantiomeric relationship is ascribed to the enantiospheric orbit of stereoisomers.

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53 A proligand is defined as a structureless ligend with chirality/achirality.[54] When a skeleton is substituted by such proligands, the resulting object is called a promolecule.[54]
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64 The symbol $\mathbf{S}^{[4]}$ is used to designate the symmetric group of *degree* 4, while the symbol $\mathbf{S}_4$ is used to designate the cyclic subgroup of *order* 4 in the series of the subgroups of the point group $\mathbf{T}_d$. They are completely different from each other. Moreover, do not confuse the symbol $\mathbf{S}_4$ with the symbol $\mathbf{S}_4^{[4]}$, which is used to designate the cyclic subgroup of order 3 in the series of the subgroups of the symmetric group $\mathbf{S}^{[4]}$.
65 Although the term "enantiomorphic" has been proposed to designate the relationship between ligands in isolation,[38] the term "enantiometric" is used in the present paper.
66 The conventional term for this type of non-equivalence is "diastereotopic." In the present approach, two sites in a diastereotopic relationship are characterized by distinct coset representations of the same kind assigined to them.
67 Although a reflection operation converts a chiral molecule or promolecule into its enantiomer (mirror image), the operation requires no bond breaking.
68 This type of equivalence classes is called *orbits of stereoisomers*, which are controlled by CRs in a similar way of orbits of ligands. See the discussion described bellow.
69 This term "stereoisomer" is used to designate homomers, and enantiomers, and diastereomers in the same manner as the conventional usage. The term "stereomer" is used to designate homomers and enantiomers, which are equivalent on the action of a point group.
70 A permutation operation converts a chiral molecule or promolecule into its enantiomer (mirror image), where the operation necessitates bond breaking. For example, Walden's inversion of a chiral molecule is formulated by a permutation operation.
71 A proper or improper rotation of a point group acts on on the vertices of a tetrahedral skeleton through the corresponding coset representation. Then, a proligand of the same kind is placed on each vertex with the same numbering, where the chirality of the proligand is inverted for improper rotations.
72 See Chapter 15 of Ref. 56.
73 We once referred to this fact in our correspondence with a parody of a famous Greek myth (R. Warner, "Men and Gods," Kenkyusha, Tokyo, 1959): An organic chemist demanded to know the riddle and the Sphinx said "What is it that controls elements in a group, controls atoms in a compound, and finally isomers in organic chemistry?"
"Is it a coset representation or a mark?" replied the organic chemist. The Sphinx found that her riddle was at last answered and died as was fated. The organic chemist received his reward and he was made King of the heaven. See Ref. 74.
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75 It is accidental that an odd permutation corresponds to an improper rotation. In general, an odd or even permutation can correspond to an improper rotation.
76 The concrete form of the coset representation $\mathbf{T}_d(/\mathbf{C}_{3v})$ has been reported in Ref. 60.
77 A permutation of a purmutation group acts on the vertices of a tetrahedral skeleton. Then, a proligand of the same kind is placed on each vertex with the same numbering, where the chirality of the proligand maintains.
78 The set of twenty-four promolecules (**12**, **13**, etc.) is controlled by a coset representation, which is, in this case, determined to be $\mathbf{S}^{[4]}(/\mathbf{S}_3^{[4]})$. The local symmetry (stabilizer), i.e., $\mathbf{S}_3^{[4]}$, corresponds to the permutation-group symmetry of the promolecule.

See Chapter 15 of Ref. 56.

79 If the numbering is strictly taken into consideration, the ABpp$\bar{}$ (**4**) cannot be converted into the AB$\bar{p}$p (**5**) on the action of the permutation group $\mathbf{S}^{[4]}$ (Fig. 6). This troublesome situation can be overcome by considering a pair of **4** and **5** in place of **4** only. However, the same result can be obtained by considering **5** to be identical with **18** as shown in the text.

80 The set of twenty-four promolecules (**4** etc. along with **18**, **19**, **20**, etc.) is controlled by a coset representation, which is determined to be $\mathbf{S}^{[4]}(/\mathbf{S}_1^{[4]})$. The local symmetry (stabilizer), i.e., $\mathbf{S}_1^{[4]}$, corresponds to the permutation-group symmetry of the promolecule. See Chapter 15 of Ref. 56.

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87 The two halves of an enantiospheric orbit in a (pro)molecule are interchangeable by improper rotations. A member of one half is called an *enantiotope* with respect to a member of the other half of the enantiospheric orbit in the (pro)molecule. The relationship between the two halves (enantiotopes) of the enantiospheric orbit is defined as being *enantiotopic*. See Ref. 34.